EFFECT OF MICRO AND MACRO NUTRIENT SUPPLEMENTATION ON THE OUTCOME OF DISEASE IN ADOLESCENTS WITH HIV ON HAART: A RANDOMISED DOUBLE BLINDED CLINICAL TRIAL

A DISSERTATION SUBMITTED TO THE TAMILNADU DR. MGR MEDICAL UNIVERSITY CHENNAI FOR THE MD DEGREE IN PAEDIATRICS APRIL 2016.

CERTIFICATION

This is to certify that the dissertation titled **"EFFECT OF MICRO AND MACRO NUTRIENT SUPPLEMENTATION ON THE OUTCOME OF DISEASE IN ADOLESCENTS WITH HIV ON HAART: A RANDOMISED DOUBLE BLINDED CLINICAL TRIAL"** is a bona fide work done by Dr. P. Blessy Sucharita in the Department of Child Health, Christian Medical College and Hospital, Vellore in partial fulfilment of the degree of MD (Paediatrics) Examination of The Tamil Nadu Dr. M.G.R Medical University, to be held in April 2016.

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DECLARATION CERTIFICATE

This is to certify that the dissertation titled **"EFFECT OF MICRO AND MACRO NUTRIENT SUPPLEMENTATION ON THE OUTCOME OF DISEASE IN ADOLESCENTS WITH HIV ON HAART: A RANDOMISED DOUBLE BLINDED CLINICAL TRIAL"** which is submitted by me in partial fulfilment towards M.D. Pediatrics Examination of the Tamil Nadu Dr M.G.R. University, Chennai to be held in April, 2016 comprises only my original work and due acknowledgement has been made in text to all material used.

SIGNATURE:

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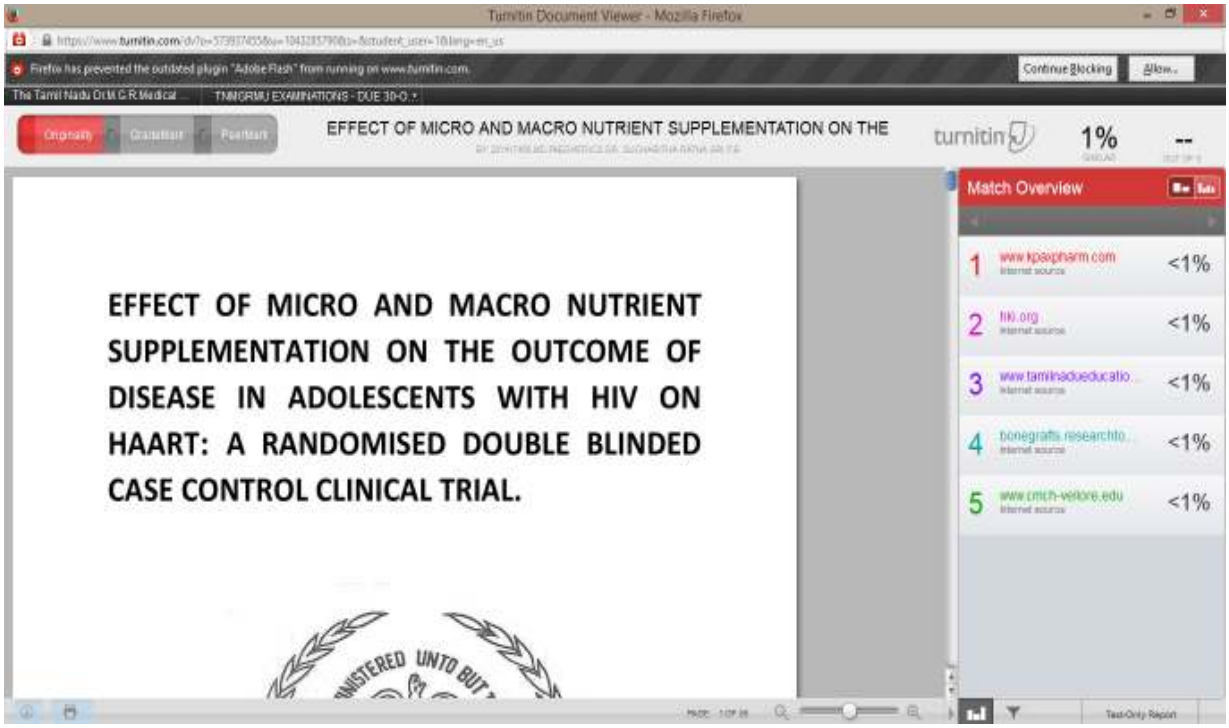
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EFFECT OF MICRO AND MACRO NUTRIENT SUPPLEMENTATION ON THE OUTCOME OF DISEASE IN ADOLESCENTS WITH HIV ON HAART: A RANDOMISED DOUBLE BLINDED CASE CONTROL CLINICAL TRIAL.

ABSTRACT:

Title

Effect of nutritional supplementation on disease outcome in adolescents with HIV on HAART: a randomised double-blinded clinical trial

Department: Department of Paediatrics, Christian Medical College, Vellore

Name of the candidate: P. Blessy Sucharita

Degree and Subject: MD Paediatrics

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Background: Adolescents with HIV (Human immunodeficiency virus) / AIDS (Acquired immunodeficiency syndrome) are a unique group of patients. During adolescence due to the growth spurt and increased activity, there is a need for increased calorie requirement and this is more so for adolescents living with HIV. There is a high prevalence of nutrient deficiencies among children, adolescents and adults with HIV. Nutritional supplementation is an easy and inexpensive adjunctive therapy to antiretroviral therapy. Nutritional supplementation can delay disease progression and improve clinical outcome in adolescents with HIV in both the developed and developing countries. Micronutrient and macronutrient supplementation among adolescents with HIV has been studied by several scientists in different countries. However, many centres in India catering to adolescents with HIV do not emphasize on the importance of nutritional supplementation along with HAART (Highly active anti-retroviral

therapy. This randomised clinical trial (RCT) was done to emphasize on nutritional supplementation in addition to good compliance with HAART.

OBJECTIVES:

1) To assess the effect of micronutrient and macronutrient supplementation on the outcome of illness among adolescents with HIV on HAART, at the end of three months and six months using the following parameters:

a) Immunological outcome - CD4 lymphocyte count levels

b) Nutritional status - Weight, Height and Body mass index centiles

c) Quality of life - Number of episodes of illness over the 6 month period

2) SETTING: a) Adolescent Medicine Clinic, Paediatrics Unit 3

b) Paediatrics Infectious diseases Clinic

c) Infectious diseases clinic, CMC

d) ACTFID (ART centre ACC – CMC trust for infectious diseases) ART centre, CMC Vellore and ID clinic, CMC, Vellore.

3) METHODS: This study was a prospective, randomized, double-blinded, clinical trial

All these patients who were eligible to be enrolled into the study had been on some nutritional supplementation containing 65 calories and 3.2 gm of protein per day, in addition to their daily dietary intake. The study participants were randomized into two

arms of 40 each, the Supplementation arm and the Placebo arm. Supplementation arm received an additional macronutrient supplementation of 400 calories and 15gms of protein per day and multivitamin tablets containing micronutrients. Placebo arm received similar appearing powder with 100 calories and 2 gm of protein per day and a placebo tablet which was similar in appearance to the multivitamin tablets. Baseline information about the nutritional status of the participants included the following:

a. Weight,

b. Height

c. BMI

d. Daily dietary intake using the 24 hour recall method

e. CD4 counts,

f. Number of illness episodes in the previous 6 months were documented.

Reassessment of the participants including weight, height and BMI centiles were done at the end of three months and six months of starting the intervention. Likewise CD4 counts were done at the end of 3 months and 6 months as part of standard care.

RESULTS:

Eighty adolescents were recruited for the study and followed up at the end of 3 months and 6 months. There was no rise in CD4 levels at the end of 3 months or at the end of 6

months. BMI in the supplementation group increased from 16.5 to 17.5 as compared to an increase to 16.5 from 16.3in the placebo group (p value - 0.036).

There was a decrease in triglyceride levels from 99.2 to 81 in the supplementation group (p value - 0.028). There was an increase in hemoglobin in the supplementation group which was not statistically significant.

Number of episodes of illness decreased from 32.5% to 0 in the supplementation group and from 20% to 2.9% in the placebo group.

CONCLUSIONS

Nutritional supplementation in adolescents with HIV on HAART is essential for good outcome in terms of weight and body mass index in turn, which is an important predictor for improvement in HIV / AIDS. The number of episodes of illness can be reduced in these patients with better nutrition.

Keywords: HAART, nutrition, outcome

ACKNOWLEDGEMENT

Above all I thank my God Almighty for enabling me to pursue this degree and to complete this thesis.

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INTRODUCTION

INTRODUCTION

In the management of adolescents with HIV / AIDS, highly active antiretroviral therapy (HAART) which aims at viral suppression, does not always result in complete immune recovery. The relationship between viral suppression and immune recovery is dynamic. Immune recovery involves several factors such as stage of disease and socio economic factors. Of the socioeconomic factors, current nutritional status plays a pivotal role.

Studies have revealed a high prevalence of nutrient deficiencies among children, adolescents and adults with HIV. Nutritional supplementation can be an easy and inexpensive adjunctive therapy to delay progress of disease and to improve clinical outcome in patients living with HIV / AIDS in both developed and developing countries. Micronutrient and macronutrient supplementation among adolescents with HIV has been studied in several countries.

However, many centres in India catering to adolescents with HIV do not emphasize on the importance of nutrient supplementation along with HAART. In order to study the effect of nutritional supplementation in addition to good compliance with medications, we proposed to do an interventional study among this group of patients.

The primary aim of this study was to observe the effect of supplementation for a 3 month period with both micronutrients and macronutrients. CD4 lymphocyte counts and other parameters were to be assessed at the end of 3 months and at the end of 6 months. The secondary objective was to document increase in weight, height, and body

mass index centiles. A third objective was to assess quality of life in terms of number of episodes of illness and hospitalizations during the 6 month period.

AIM:

To study the effect of nutritional supplementation on adolescents with HIV on HAART.

OBJECTIVES

1)To assess the effect of micronutrient and macronutrient supplementation on the outcome of illness among adolescents with HIV on HAART at the end of three months and six months using the following parameters:

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REVIEW OF LITERATURE

REVIEW OF LITERATURE

INTRODUCTION:

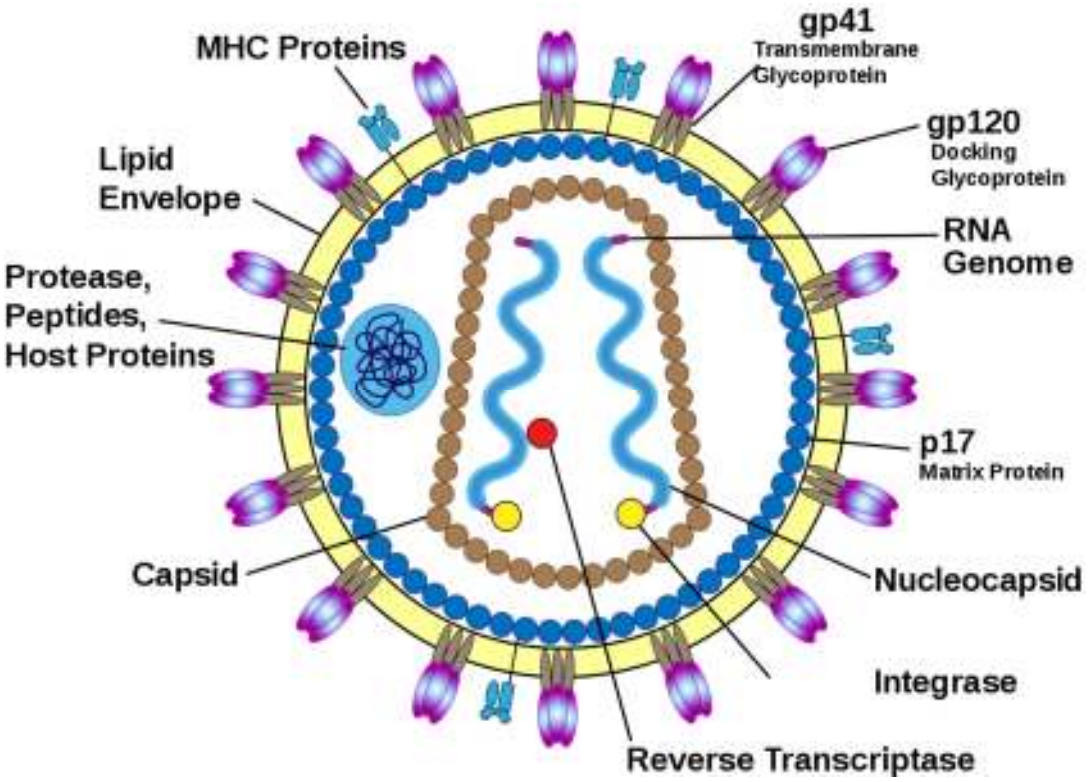
HIV / AIDS has become one of the leading causes of mortality for humanity since its discovery in the 20th century(1). It has devastated individuals, families and communities leaving millions homeless and helpless(2). It also comes with a significant social stigma and has therefore resulted in the effacement of the social order. This is because it has not only caused ill effects on a patient's health, but also on their social and psychological status, undermining their ability to function as healthy individuals and families. It has stunted economic growth of society, by increasing the demands on a person as well as by reducing their working and earning capacity in a society(3). It is said to be one of the most destructive and disabling of diseases that ever affected humanity(4).

HISTORY OF HIV**:**

The origins of HIV is unclear. It was discovered in the 1950s and so is a relatively recent disease(5). In 1959, it was first identified in a man from the Belgian Congo(6). The HIV virus is similar to the African monkey virus. Since monkeys were a source of food for the bush hunters of Africa, it is considered that the monkey virus eventually infected humans. Eating the infected meat was found to be the source of infection in these men(7). Phylogenetic studies indicate a close relationship between HIV1 and Simian immunodeficiency virus (SIV) from the chimpanzee (SIVcpz). HIV2 is related to the Sooty Mangabey monkeys (SIVsm)(8). HIV-1 and HIV-2 share many similarities in terms of their genetic makeup, transmission and clinical profile(9). AIDS is a viral zoonosis. HIV1 is responsible for the widespread pandemic. HIV 1 and HIV2 differ in

the rapidity of their transmission and the area to which they are confined. HIV2 is milder in transmission and slower to progress to the disease of AIDS when compared to HIV1(10)

HIV STRUCTURE AND MECHANISM OF TRANSMISSION



HIV is a lentivirus, belonging to the family Retroviridae. It is 120 nm in diameter, spherical with a cylindrical nucleoid and surrounding proteins (11). The nucleoid has core proteins p24 and p17. A lipid bilayer envelop ensheaths the viral body. The envelop proteins are gp41 and protein gp120 that aid in binding to target cells. Viral genome RNA and the reverse transcriptase enzyme are within the nucleoid. The genetic material in the retrovirus is in the form of RNA(12). This is transcribed into DNA by the enzyme reverse transcriptase. The DNA thus produced migrates into the nucleus of the host cell

and is inserted into human genome by the enzyme integrase, thus infecting the human(13).

BURDEN OF HIV

HIV/AIDS in earlier days because of the high mortality rates, caused severe damage to food safety of societies and nations. The constraints caused on the economic situation led to financial instability and further affected the nutritional status of the patients. The health system worldwide has been challenged significantly by HIV / AIDS in the last 30 years(14). This is more so in the poorer and socially deprived sections of society(15). While success in slowing the disease is evident in some parts of the world, there are other parts where it is still a severe crippling disease(16). The hard earned success and development in science and medicine over the previous half a century was wiped away by the incomparable mortality and morbidity associated with HIV(17). The overall quality of life for a person is adversely affected(18). Coping with the deteriorating health needs, drug effects of ART, social stigma, guilt, fear of death from AIDS related illnesses and economic hardships can worsen the situation further(19).

Within families, relationships are severely affected as a result of HIV(20). Chronic illness in parents affects their ability to care for and support their children and other family members. Guilt, shame, anger and poverty stunt family relationships and cause psychological trauma to children(21).

GLOBAL DISTRIBUTION:

HIV / AIDS stands number five in the list of leading causes of disability in the world (22). Since the origin of the epidemic, there are 78 million people infected with HIV. Every year an alarming 2.1 million new people are infected and 1.5 million die due to AIDS related diseases(23). Every part of the world is affected by the HIV pandemic; there are some areas which are more affected than the others. Sub Saharan Africa has been the worst affected by this disease where 70% of the population is infected(24). A majority(90%) of persons living with this disease, live in poor, unindustrialised and underdeveloped countries of the world(25). Distribution of HIV is unequal, with around 930,000 people being affected in North America while in Sub-Saharan Africa an estimated 26 million are affected. It is evident that HIV is more concentrated in areas which are already deprived of a stable economy and are therefore already facing serious health related problems(15).

HIV IN INDIA:

India stands third among all countries with regard to HIV / AIDS(26). In India, AIDS pandemic began in the mid-1980s. The first case was identified in Chennai. Within the country, prevalence is widely variable. The states of Tamil Nadu, Andhra Pradesh, Telangana and Karnataka are home to 3.6 lakh patients with HIV / AIDS, constituting 50% of the total number in India. Of the 7.7 lakh patients in India, Tamil Nadu is home to 80,685(27).

HIV IN ADOLESCENTS:

The WHO defines the adolescent age arbitrarily as 10-19 years. In India 22% of the national population is in the adolescent age group of 10-19 years (31). Worldwide adolescents represent 25–30% of all persons living with HIV / AIDS, constituting 9–10 million patients (28). It is estimated that 45% of new HIV infections occurred in the 13-22 year age group every day (29). According to UN General Assembly, adolescents constitute half of the new cases of HIV occurring daily worldwide (30).

Adolescents living with HIV are of two main categories, students and slum/street youth. Street dwelling youth are a vulnerable group at risk for acquiring HIV. IV drug abuse, unsafe sexual practices, serial monogamy as well as multiple sexual partners are some of the factors which play a key role in the transmission of HIV in adolescents(32). Ignorance about safe sex, is one of the common causes of HIV prevalence among adolescents(33). Adolescents with HIV/ AIDS comprise a diverse group of patients in terms of socio-demographics, the mode of transmission, clinical profile, associated substance abuse, sexual activity, immune status, psychological development and their adherence to anti-retroviral therapy(ART)(34).

Several studies have been done in different parts of the world looking for probable risk factors among adolescents with HIV / AIDS. In the streets of Kathmandu, Nepal, prevalence of HIV among adolescents is 20 times higher than in the general population. Risk factors in these adolescents include IV substance abuse, multiple sexual partners and commercial sex workers (35).

CHALLENGES IN DEALING WITH ADOLESCENTS WITH HIV

Adolescence is a critical stage in human development (36). It is a transition from a dependent childhood to an independent adulthood. During this period there is an increased vulnerability to sexual ill health (37). Geldard and Geldard (2006) understood that it is a stage of travel from dependency to independence, autonomy to maturity and a stage where an individual moves from family support to other supports in the social system (38).

In the UK, paediatric oncologist Maria Michelagnoli and her colleagues coined the phrase “The Lost Tribe” to describe adolescents who were in their care. This was because, adolescents in their research population when compared to the 2 year olds with leukaemia and the 70 year olds with lung cancer, required age specific strategies to improve their compliance and the resultant outcome of illness (39).

HIV in adolescents needs to be dealt differently from HIV in adults (40). Identifying themselves with the illness is a big challenge for adolescent patients. Other factors that further worsen this situation are the need for lifelong medication, the social stigma and the loss of loved ones to HIV / AIDS (41). Their self-esteem is affected by apprehension regarding their future with regard to education, career and marriage and the feeling that they are affected for a lifetime (42). WHO working group on HIV / AIDS has clearly outlined the need for a holistic approach in the management of adolescents living with HIV, which is to be patient based and family cantered (43). Research in the recent years has stressed on the importance of the role of family in preventing HIV in adolescents.

Family is the most important unit responsible for moulding the life of an adolescent (44). Healthy family relationships, open communication, good education, secure peer groups, support and affection are needed for adolescents to grow up into overall healthy individuals (45).

MALNUTRITION IN HIV:

There is a higher prevalence of malnutrition in patients with HIV/AIDS as a result of a poor appetite, decreased intake and increased demands. Malnutrition in turn plays an important role in the outcome of illness (46). Weight loss is one of the earliest and commonest features of AIDS (47). Chlebowski et al in their study among hospitalised HIV patients, observed that almost all patients had a weight loss of 10% or more (48). Weight loss, emaciation and low BMI are indicators of HIV, hence the name Slim disease. Sixty percent of adolescents with HIV have clinical findings suggestive of Slim disease (49). Three important factors of poor nutrition, malabsorption and less affordability result in an overall dismal nutritional status and a bad outcome of illness (50). Diarrhoea and malabsorption are common complaints in 30–50% of HIV patients in developed countries and in 90% of those in developing countries (51). In addition, while on ART, these patients suffer from decreased appetite because of an altered taste, exaggerated nausea and vomiting. Depression, guilt, poor socioeconomic conditions and non-affordability of nutritious food are also important factors contributing to the under nutrition in HIV/AIDS (52). Abnormalities in endocrine function like adrenal insufficiency, lipodystrophy, diabetes can also contribute to poor nutrition, in HIV patients (53).

MICRONUTRIENT DEFICIENCY IN HIV

HIV infected patients have more micronutrient deficiencies when compared with the general population (54). Deficiencies in thiamine, selenium, zinc, and vitamins A, B-3, B-6, B-12, C are individually responsible for poor immunity, increased morbidity, mortality and disease progression in patients with HIV (55). Randomized, open labelled trials were conducted to assess the effect of micronutrient supplementation in these patients both by supplementing individual nutrients as well as combined elements. It was observed that there was a significant increase in antioxidant induced defence mechanisms and decrease in oxidative stress after supplementation. However, CD4 levels and viral loads were not affected significantly (56).

MACRONUTRIENT DEFICIENCY IN HIV

Protein energy malnutrition is the outcome of macronutrient deficiency in patients with HIV. Increased IL1, IL26 and TNF alpha levels cause poor appetite. Recurrent GI tract infections results in malabsorption in these patients. Drug toxicity due to antiretroviral therapy causes disabling constitutional side effects including nausea and vomiting(57). In addition, food insecurity and the resultant protein energy malnutrition are major hindrances to effective treatment of patients with HIV. Malnutrition in turn leads to disease progression and a worse clinical outcome (58). Food insecurity has also been shown to prevent adherence to treatment (59). It is understandable that a family which does not have enough food to eat would be less inclined towards ensuring compliance with medicines.

There are a few studies on the effect of macronutrient supplementation and more on that of micronutrient supplementation. These studies were carried out for time periods ranging from 3 weeks to 6 months. Rebenek et al in the USA, conducted a randomised control trial in 118 patients with HIV in the age group 13-22 yrs. The control group received a lipid based diet and the placebo group received diet counselling alone. At the end of 12 weeks, there was a significant increase in lean body mass, weight and height in the intervention group; but, there was no increase in viral loads or CD4 levels.

A review of 12 RCTs was carried out where, 4 involved amino acid supplementation, 6 with amino acid, calories and protein supplementation and 2 on just carbohydrate supplementation. This review revealed that macronutrient supplementation had a more significant impact on the protein and energy intake in the intervention group than in the placebo group. There was no effect on CD4 levels or viral loads except in 1 out of the 12 studies (60). WHO guidelines on nutritional recommendations in patients living with HIV / AIDS include an increase in daily energy by 10% in asymptomatic patients and by 20-50% in symptomatic patients which happens during a flare in disease. Proteins is to constitute 15% of the total calorie intake (61).

EFFECTS OF MALNUTRITION ON HIV

There is an intricate correlation between nutritional status and HIV infection. Poor nutrition per se, in general has an adverse effect on immunity. This effect is exaggerated in patients with HIV. The disease condition, severity and the response to therapy are all affected by nutritional status (62). Quality of life and lifespan are significantly influenced by the state of nutrition (63). A retrospective cohort study done by Paton et al on adolescents with HIV attending a referral centre for HIV in Singapore, concluded

that malnutrition at the start of ART had a significant association with decreased survival. This study emphasises the need for nutritional supplementation as an adjuvant to ART for better outcome (64). In spite of the advances in medical management in the form of ART, malnutrition per se can hasten progression of disease (65). Understanding that malnutrition is the cause of poor outcome in HIV, is a big leap in the management of HIV (66). In any illness, starvation leads to increased morbidity. Starvation is also due to the effect of underlying disease. In HIV, the morbidity during starvation is independent of underlying disease (67). Starvation by itself causes morbidity and this is independent of the CD4 levels or immune status. A weight loss of 10-15% in itself is a poor prognostic factor. In 3 studies that were conducted in adolescents, the effect of wasting leading to increased hospitalisations and morbidity was independent of CD4 levels (68).

EFFECT ON IMMUNITY:

Severe malnutrition is the commonest cause of immunodeficiency worldwide (69). Presence of malnutrition before initiating ART is an independent indicator of mortality in HIV (70). Malnutrition, the lowered immunity and the infectious disease are interlocked in a complex negative cascade (70, 71). In children, protein energy malnutrition causes widespread atrophy of the lymphoid tissues. This is seen mainly in the T lymphocytic area of the tissues (72). One of the biggest lymphoid organs involved in immunity is the gastrointestinal tract. HIV infection causes flattening of the intestinal villi thereby decreasing effective D-xylose absorption. Both carbohydrate and fat absorption are affected. There is a resultant deficiency of fat soluble vitamins like vitamin A and E which are essential for immunity (73). Chandra et al, report that in

patients living with HIV who also have protein energy malnutrition (PEM), there is reversal of T helper: suppressor cells and depletion of total T lymphocytes. PEM also leads to mitigation of the function of killer T cells in combating the various infections (74). Post mortem studies on malnourished HIV patients revealed that there was a profound loss of cell mediated immunity due to depletion of the thymic lymphatic system (75). Proteins that are involved in the production of cytokines, complement proteins, kinins, clotting factors and certain enzymes related to immunity are all deficient in patients with HIV, due to a deficiency in aminoacids (76)(77).

In patients with HIV / AIDS, the two common concerns are weight loss and wasting. These are important factors closely linked with decreased CD4 counts, the most important predictor of death related to HIV (78). Several trials have been carried out to look at the effects of micronutrient and macronutrient supplementations on CD4 levels, viral loads and disease progression. A review of all the 31 trials done in the last decade revealed that out of the total of 31 trials, 9 were conducted using micronutrient supplementation and 22 with macronutrient. The review concluded that, only 11% of the studies using macronutrient supplementation as intervention and 36% of those using micronutrients have resulted in any increase in CD4 levels. The viral load is decreased in only 33% of the studies using macronutrients and 12% of those using micronutrients. This suggests a limited impact of nutritional supplementation on CD4 counts. However, the studies that were included in the review had several limitations such as differences in the study design, study population, dosage of supplements used, baseline nutritional and CD4 status, clinical condition, and ill-defined end points. There is a need for larger studies to draw conclusions regarding this problem (79).

Mangili reported in their RCT among 59 patients who were randomised to receive either protein supplements or placebo, that the intervention group which had received proteins showed a significant increase in CD4 counts by 31 cells/mm^3 indicating a beneficial effect of nutrient supplementation on immunity in patients with HIV. Sowmya Swaminathan in her study on children with HIV in southern India reported a significant enhancement in growth, weight, BMI and immunity of patients with critical illness, when supplemented with micronutrients (80).

WEIGHT, HEIGHT, BMI CHANGES IN HIV

Weight loss in HIV leading to wasting is a commonly encountered problem in untreated HIV / AIDS and is evident at any time during the course of infection. It needs to be addressed immediately as it could be due to an active disease or due to a superadded infection. Loss of lean tissue mass leads to increased mortality whereas loss of muscle protein mass leads to depleted functional status (65).

Currently ART is not only efficient in curbing replication of the virus and restoring immune function, but also helpful in faster weight gain when given along with a balanced and nutritious diet (81). Therefore not just ART, but nutritional counselling in addition will help in improving BMI which an important predictor of mortality in HIV (82). Donald Hovfer et al in their studies among HIV infected men reported a much faster weight gain in seronegative men than expected in comparison to seropositive men. Their study also concluded that HIV1 seroconversion is associated with a significant weight loss. And the weight loss relating to mild and moderate HIV can be evident as early as 12-18 months before the diagnosis of HIV (83).

Mortality risk increases in those with HIV on HAART if their lean body mass is low. Therefore careful monitoring of BMI in adolescents is important in patients with HIV. This might require both macronutrient and micronutrient supplementation using fortified, blended foods (84). Evans et al conducted a randomised controlled trial where, in one arm patients were given a supplement termed 'Future life porridge' containing 388 kcal/day along with ART and in the other arm only ART. At the end of 6 months a significant increase in weight, height and BMI was reported (7.8% vs 5.5%; $p = 0.007$) (85).

LIPID CHANGES IN HIV

Patients with HIV have lipid changes occurring in their body due to two reasons. Firstly, ART causes lipodystrophy leading to lipid disturbance and redistribution. This is true with all protease inhibitors and drugs belonging to certain other groups (86). Secondly, fat malabsorption is seen in 30% of asymptomatic individuals (87). Micronutrient deficiency contributes to viral multiplication which induces a number of metabolic alterations such as hypertriglyceridemia and increased de novo synthesis of fatty acids by the liver (88).

Safrin Sharon et al in their study first defined the term lipodystrophy in patients with HIV reporting redistribution of fat to specific regions in the body(89). HIV-associated lipodystrophy syndrome (HALS), is a well described adverse effect of HAART. It includes characteristic clinical features of either lipoatrophy or hyperadiposity in certain regions. More importantly, this is associated with insulin resistance and the metabolic syndrome (90).

Grunfield et al in their study on estimation of triglyceride levels in 32 HIV positive patients observed that triglyceride (TG) levels were high in HIV positive patients on HAART when compared to the control who were not on HAART group ($p < 0.002$ and $p < 0.005$, respectively) (91). Protease inhibitors, Indinavir and Lopinavir caused an increase in both cholesterol and triglyceride levels. NRTIs like Stavudine and Zidovudine caused lipoatrophy and hypertriglyceridemia (60). Cardiovascular complications were demonstrated in Abacavir (92). Use of more than one protease inhibitor doubled the likelihood of hypertriglyceridemia when compared with use of a single protease inhibitor (93).

Several studies were carried out to look into how best nutritional supplementation can be utilised to deal with this problem. Evidence for its role is still under review (90). Margo Woods et al in their RCT, using nutritional supplementation for a period of 3 months concluded that the levels of triglycerides in the intervention group at the end of 3 weeks and 13 weeks showed a significant decrease from a median of 180mg/dl to 114 mg/dl(p value 0.003) (94). It was concluded that there is decline in arachidonic acid, phospholipids and the process of lipogenesis relating to the metabolic syndrome.

ANEMIA IN HIV

Anemia in patients with HIV / AIDS has a deleterious effect on overall health as well as their functioning capacity (95). Parinitha et al studied the relationship between HIV and hematological changes, to primarily detect possible hematological changes in HIV / AIDS and their correlation with CD4 levels. Two hundred and fifty patients had complete blood counts and CD4 levels. Of the 250, 84% had normocytic normochromic anaemia. It was noted that a severe immunocompromised state with CD4 $<200/mm^3$

was associated with a higher incidence of anaemia. They concluded that treatment of haematological abnormalities will decrease the associated morbidity(96). Anaemia while on HAART especially on a zidovudine containing regimen is of concern and needs careful monitoring (97). It occurs in about 30% of asymptomatic patients and 77% of those with established AIDS. It is associated with declining quality of life and increasing mortality (98).

MANAGEMENT OF HIV

Two important caveats to the management of patients with HIV / AIDS are: a) good compliance with antiretroviral therapy (ART) to prolong life and halt the spread of HIV / AIDS and b) optimal nutrition that is essential for health (99). The challenge is to apply both these principles of clinical care and nutrition science in the management of people living with HIV / AIDS (100).

Highly active antiretroviral therapy (HAART) results in significant improvement in clinical outcomes. However, risks of opportunistic infections and mortality are still high and immune recovery that is expected with HIV after the initiation of HAART is inadequate (101). As in most chronic illness, micronutrient and macronutrient deficiencies are commonly observed with HIV / AIDS. These deficiencies have been associated with an increased rate of disease progression and mortality (102).

Several studies have reported a high prevalence of nutritional deficiencies among this group of patients (103). These deficiencies are associated with frequent opportunistic infections, faster disease progression and a higher incidence of HIV-related mortality

(49). Possible mechanisms include increase in intracellular oxidative stress, increase in viral replication and a significant reduction in the number of CD4 lymphocytes; studies have revealed that these findings are associated with both individual nutrient deficiencies and in combined deficiencies (104). These mechanisms either alone or in part, may result in increased morbidity, rapid disease progression, and a high rate of mortality observed in adolescents with HIV (105). Research on micro and macronutrient deficiencies and the role of their supplementation in adolescents with HIV receiving HAART has now become an important strategy to consider in the management of adolescents with HIV / AIDS (106). Nutritional supplementation using different compositions have been studied over the past decade, among different populations of patients with HIV / AIDS on HAART, such as children, adults and pregnant women. These studies reveal enough evidence that nutritional supplementation has a direct effect by increasing body mass index and CD4 lymphocyte numbers, decreasing viral load and thus delaying disease progression.

Kaiser et al in their randomized controlled trial observed that the absolute CD4 count increased by 24% in the intervention group receiving micronutrient supplementation for 12 weeks. There was 0% change in the placebo group ($P = 0.01$). The mean HIV-1 RNA decreased in the intervention group (107). Fawzi et al in their study of 1071 pregnant women with HIV on HAART reported a significant increase in CD4, CD8, and CD3 counts with multivitamin supplementation (108).

Such studies on nutritional supplementation as an adjunct to HAART have not been carried out in the adolescent age group. Also there are no studies which reported on the sustained effect of nutritional supplementation after discontinuation of the nutrients.

Also in the Indian subcontinent interventional studies among adolescents per se were few.

Worldwide there are 9–10 million adolescents/young adults infected with HIV (109). Adolescence is a critical stage in human development (110). Nutritional support and healthy lifestyle choices will have a positive impact on adolescents in general and especially those on HAART (111). This RCT was proposed to assess the beneficial effect of nutritional supplementation if any, while managing adolescents with HIV/ AIDS. If proven to be of significant benefit, nutritional supplementation is a cost effective adjunct to HAART for adolescents with HIV / AIDS in our community.

RECOMMENDATION FOR NUTRITION IN HIV

HIV/AIDS is complicated by the prevalence of under nutrition in the lower socioeconomic strata of society. Estimation of the level of nutrition is essential in the management of adolescents with HIV. HIV / AIDS has a negative effect on the overall health by affecting the socioeconomic conditions. There is an increased need for more energy in order to combat the viral infection. It is imperative that adequate nutrition is emphasised (112).

There is a dire need for a concerted management of both the infection and under nutrition among children and adolescents with HIV/AIDS. This would define holistic care for this special group of patients (113).

HIV in adolescents causes under nutrition on the one side and hypertriglyceridemia on the other. Hypertriglyceridemia raises the risk of cardiovascular complications

including myocardial ischemia by 50% when compared to those without HIV. And these have been associated with higher risks of progression of illness and mortality(114).

In 2005 the World Health Organisation proposed guidelines for dietary requirements in HIV patients. This group of patients require a 10% raise in energy requirement in asymptomatic patients more than the recommended diet. If symptomatic, the raise should be 20-50% more and protein should be 10-15% of the entire energy intake. Such an increase in requirements can only be met if it is supplemented on top of daily requirement. Dietary supplementation for patients with HIV play an important role in the final outcome especially in those with a BMI of <18.5. There is a six times more likelihood of death in those with poor nutrition than those who are well nourished, once HAART is initiated (115). It takes immense effort to combine medical care and the science of nutrition while managing these patients (116).

In terms of specific recommendations, overall dietary goals for adolescents with HIV are consistent with those for all adolescents and include meeting the needs of normal growth. A high-quality, nutrient-rich diet, good eating habits, avoiding obesity through limiting intake of energy dense, nutritionally poor foods, engaging in daily physical activity and avoiding substance abuse are the recommendations for adolescent health. The final aim in nutritional recommendation in adolescents with HIV is to not forget the requirements of expected growth. It is advisable to supplement macronutrients as ready to use mixtures and oil based creams with micronutrients added to it. Along with nutrient support other issues to consider include amount and duration of supplementation, other associated illnesses, economic burden on the family etc (117).

Nutritional supplementation represents a cost-effective intervention for addressing HIV / AIDS among adolescents especially in resource limited settings and this should be investigated further (118) .

RATIONALE FOR THIS STUDY

Nutritional supplementation along with HAART has been studied in past research and mostly among children, adults and pregnant women. Such studies have not been conducted among adolescents with HIV in India.

The physiology, body mechanisms, pharmacokinetics, growth spurt and nutritional requirements of adolescents is different from that of children and adults. Therefore this study focuses on the adolescent age group on whom not many studies on nutritional supplementation has been done.

Adolescents are according to WHO definition, those young persons who are 10-19 years of age. Among adolescents with HIV / AIDS, there is deficiency of micronutrients (vitamins and minerals) and macronutrients (proteins and calories). This deficiency may be related to the disease per se, the HAART drugs, poverty or other sociocultural factors. This nutritional deficiency is associated with a more rapid disease progression and increased mortality in these patients.

HAART is an effective way of viral suppression in adolescents with HIV, but immune recovery with HAART alone is known to be a slow process and therefore ineffective.

If this study reveals that micronutrient and macronutrient supplementation improves CD4 levels, BMI and decreases morbidity among adolescents with HIV living in India, it would be a cost effective way of improving their overall outcome. This knowledge

can then be translated to standard of care in the future in all the participating centres initially and help emphasize the need to implement this strategy for all adolescents with HIV.

METHODOLOGY

Design - A prospective randomised double blinded placebo controlled clinical trial

Setting

a) Adolescent Medicine Clinic
b) Paediatrics Infectious diseases Clinic
c) ACTIFID(ACC,CMC TRUST FOR INFECTIOUS DISEASES) center, ID Clinic

The setting is a tertiary care centre located in Vellore, a city in south India, at a latitude of 12.9 degrees North with sunshine throughout the year. The study was carried out over a period of 18 (only the supplementation was given for 6 months) months (January 2015-June 2015)

Participants:

Adolescents 10-19 years of age, diagnosed to have HIV and already on HAART therapy for a minimum of 6 months.

Informed Consent

Informed consent was taken from the parents as well as from the participants prior to recruitment (Patient information sheet and Sample consent form -Annexure 4 and 5).

Key criteria

a) Inclusion Criteria**:**

Adolescents from age 10-19yrs diagnosed to have HIV and already on HAART therapy for a minimum period of 6 months.

b) Exclusion Criteria:

People not falling in the age group of 10-19yrs

Intervention and Comparator agent

Intervention**:** Micro and Macronutrient supplementation with written dietary advice.

Comparator agent**:** Placebo macro and micronutrients with written dietary advice.

Ethics clearance

The study was approved by the Institutional Research Board and Ethics committee (Annexure 3)

Clinical trial registration

The trial was registered in the Clinical Trials Registry of India (Annexure 4)

METHODOLOGY

METHODOLOGY:

Enrolment started as soon as approval from IRB was obtained. 80 adolescents with HIV infection on HAART who fulfilled the inclusion criteria were enrolled in the study. All these patients had been on a baseline supplementation of 65 k calories and 3.2 gm of protein per day. The caregivers were given a written set of instructions on dietary advice for their wards. Study participants were randomized into two arms of 40 each, the Supplementation arm and the Placebo arm.

Supplementation arm received an additional macronutrient supplementation to the tune of 400 calories and 15 gm of protein per day as well as one multivitamin tablet per day containing the micronutrients. Placebo arm received a similar appearing powder with calorie content of 100 calories and 2 gm of protein per day and placebo tablet which was similar in appearance to the multivitamin tablets but not containing any micronutrients.

Baseline information about the nutritional status of the participants including weight, height and BMI centiles, the nutritional supplement they had been, baseline CD4 counts, history regarding number of illness episodes in the previous 6 months were documented. Then each patient was given 2 weeks' supply of macronutrient and micronutrients in sachets. Micronutrient supplement was given for three days a week.

Diet: 1. Macronutrient: A coarse powder made up of bengal gram, groundnuts and sugar making up to 400 calories and 15 gm of protein was made in the Dietary department, CMC, Vellore. This powder was tasted and found palatable. Sachets were given once a

fortnight to each participant in the intervention arm and continued for a period of 3 months.

2. Micronutrients: A tablet containing the following nutrients as per ICMR guidelines, weighing 0.765 gm with 1.937 kcal of energy was given:

Micronutrient	**Amount (mg/mcg)**	**% of RDA**
Vit A	600 mcg	100
Vit B1	1.2 mg	100
Vit B2	1.4 mg	100
Vit B3	16 mg	100
Vit B5	5 mg	100
Vit B6	2 mg	100
Vit C	40 mg	100
Folic acid	100 mcg	100
Methyl-cobalamine	1 mcg	100
Zinc	10 mg	100
Manganese	2 mg	100
Copper	0.9 mg	100
Selenium	55 mcg	100

Placebo macronutrient and micronutrient sachets were given to the participants on the placebo arm for a period of 3 months.

Compliance was ensured by the principal investigator (PI) making weekly phone calls to all the participants and visiting the participants once a month. A notebook was provided for the caregivers of each of these participant on which patient / caretaker could record on a daily basis whether the sachet and the tablet were taken. Weekly reminders by phone call were done to encourage compliance with taking the nutrients as well as recording in a notebook.

Reassessment of the participants including weight, height and BMI centiles were done at the end of three months and at six months of starting the study. Likewise CD4 counts were done at the end of 3 months and 6 months as part of standard of care procedure.

Data obtained was entered into an Epi data file. Analysis was done using software SPSS 16. Randomization code was known only to the dietician and was revealed to the statistician only at the time of analysis.

1. Primary outcome: Effect on CD4 levels
2. Secondary outcome: Effect on height, weight, BMI, number of episodes of illness (HIV related / unrelated) over a period of 6 months.

Target sample size and rationale:

Two Means - Hypothesis testing for two means

SD of change in CD4 count from baseline in supplementation group	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
SD of change in CD4 count from baseline in group not on supplementation	**93**	**94**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
Mean difference in change of CD4 count across 2 groups	**50**	**58.9**	**58**	**50**	**55**	**50**	**55**	**65**	**70**
Effect size	**0.518135**	**0.607216**	**0.58**	**0.5**	**0.55**	**0.5**	**0.55**	**0.65**	**0.7**
Alpha error (%)	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**
Power (1- beta) %	**80**	**80**	**80**	**80**	**80**	**90**	**90**	**80**	**80**
1 or 2 sided	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Required sample size per group	**59**	**43**	**47**	**63**	**52**	**84**	**69**	**37**	**32**
10% loss to follow-up					**64**			**45**	**40**

Reference used to select sample size: 'Micronutrient supplementation increases CD4 counts in HIV infected individuals on HAART: A prospective double blinded placebo controlled trial'. Jon D. Kaiser, Adriana M. Campa et al. J.Acquir Immune Defic Syndr 2006; 42:523-528.

The required sample size to show a change of about 70 units in the CD4 count from baseline to 3 months across the groups receiving supplementation and not receiving

supplementation was found to be 40 in each group with 80% power, 5% significance level.

i. Method of randomization: Simple Randomization

ii. Method of allocation concealment: using envelopes

iii. Blinding and masking: Blinding of key investigator, clinician, social worker and participants.

$$n = \frac{2s_p^2\left[Z_{1-\alpha/2} + Z_{1-\beta}\right]^2}{\mu_d^2}$$

$$s_p^2 = \frac{s_1^2 + s_2^2}{2}$$

Where,

s_1^2 : Standard deviation in the first group

s_2^2 : Standard deviation in the second group

μ_d^2 : Mean difference between the samples

α : Significance level

1- β : Power

Statistical Analyses:

The mean ± SD of CD4 levels was calculated at baseline and after 3 months for the groups separately, one receiving nutritional supplementation + dietary advice and the other with dietary advice only. Change in CD4 levels was calculated as the difference in CD4 from baseline to the end of 3 months. Normality assumption of the 'change' in

both the groups was checked using QQ plots. When these distributions are normal, Welch test was used to compare the 'mean change' in CD4 levels across the groups and 95% CI was calculated for the difference in the mean change. When the normality assumption was violated, permutation test and/or bootstrap was used to compare the mean change and 95% percentile bootstrap was calculated for the difference in mean change. Analysis of covariance was also used to adjust for baseline CD4 levels. If there were any baseline differences, then those baseline differences were adjusted using linear regression. Generalized Estimating Equations (GEE) was used to compare the CD4 levels across intervention groups over time (1 month, 3 months and 6 months).

b. Methods for additional analyses, if indicated.

Secondary outcomes such as height, weight were compared across the intervention groups using Welch test or bootstrap and 95% percentile bootstrap was presented for the difference of means. Number of episodes of illness was compared using Mann Whitney test and the 95% CI for the difference in medians was presented. GEE for normal distribution was used to compare height, weight across the groups over time. GEE with poisson outcome was used to compare the number of episodes of illness across interventions over time

DATA SAFETY MONITORING BOARD:

Adverse effects of the Multivitamin tablet or the Placebo used were thought to be unlikely. Therefore DSMB clearance was not obtained.

VALIDATION OF DRUG USED IN THE TRIAL

The multivitamin tablet was validated by an external laboratory. The results were not known to the investigator, treating team, the caregivers, social workers, and to the patient or their families.

Definitions:

Adolescent: A person 10 - 19 years.

Normal hemogobin levels:

Female 12.0 to 16.0 g/dl (mean 14.0 g/dl)

Male: 13.0 to 16.0 g/dl (mean 14.5 g/dl)

Normal Triglycerides level:

Normal: Less than 150 mg/dL

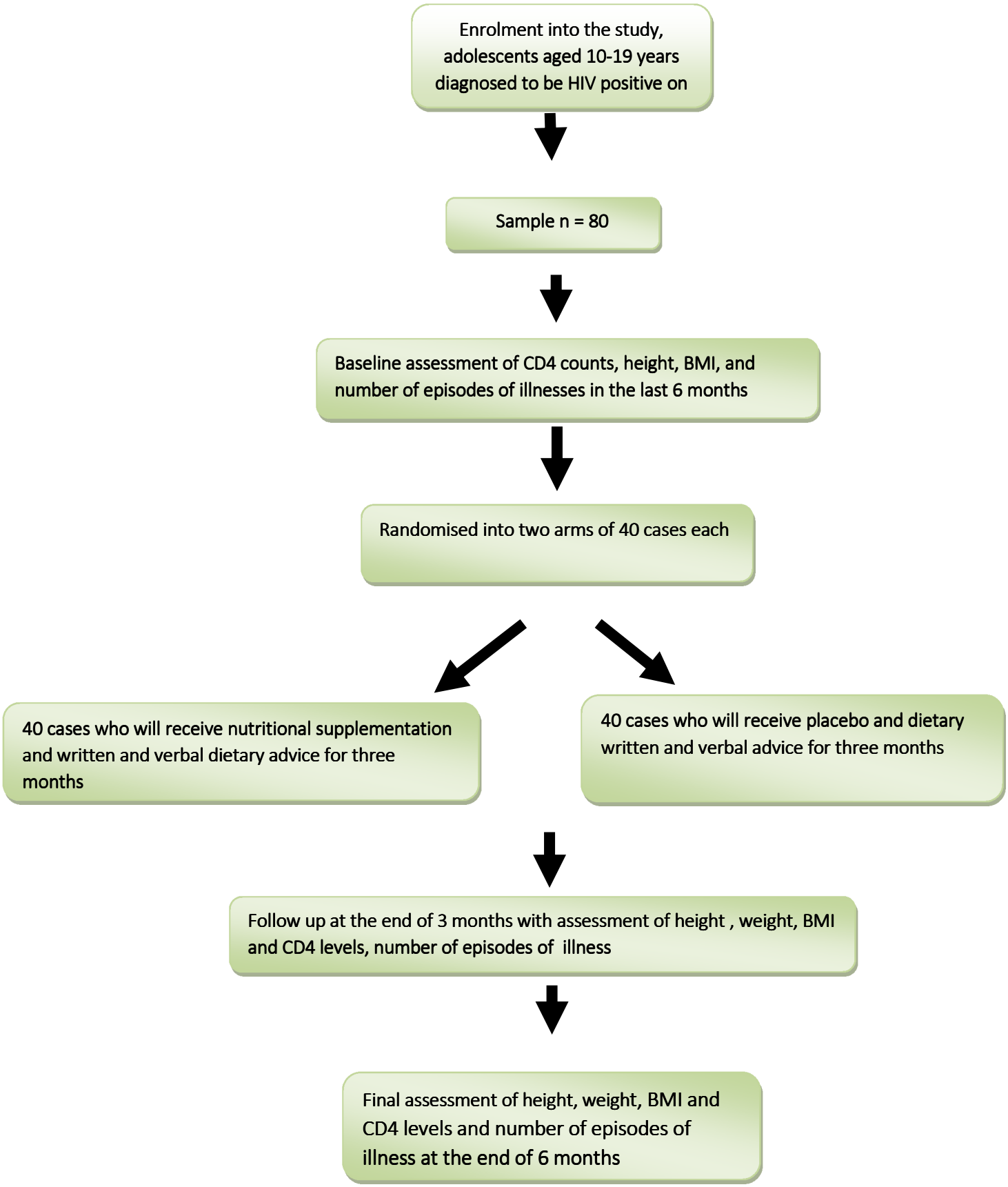
Borderline High: 150 - 199 mg/dL

High: 200 - 499 mg/dL

Very High: 500 mg/dL or above

Normal CD4 count - 500–1,200 cells/mm^3 in adolescents.

Detailed diagrammatic Algorithm of the study



RESULTS AND ANALYSIS

RESULTS AND ANALYSIS

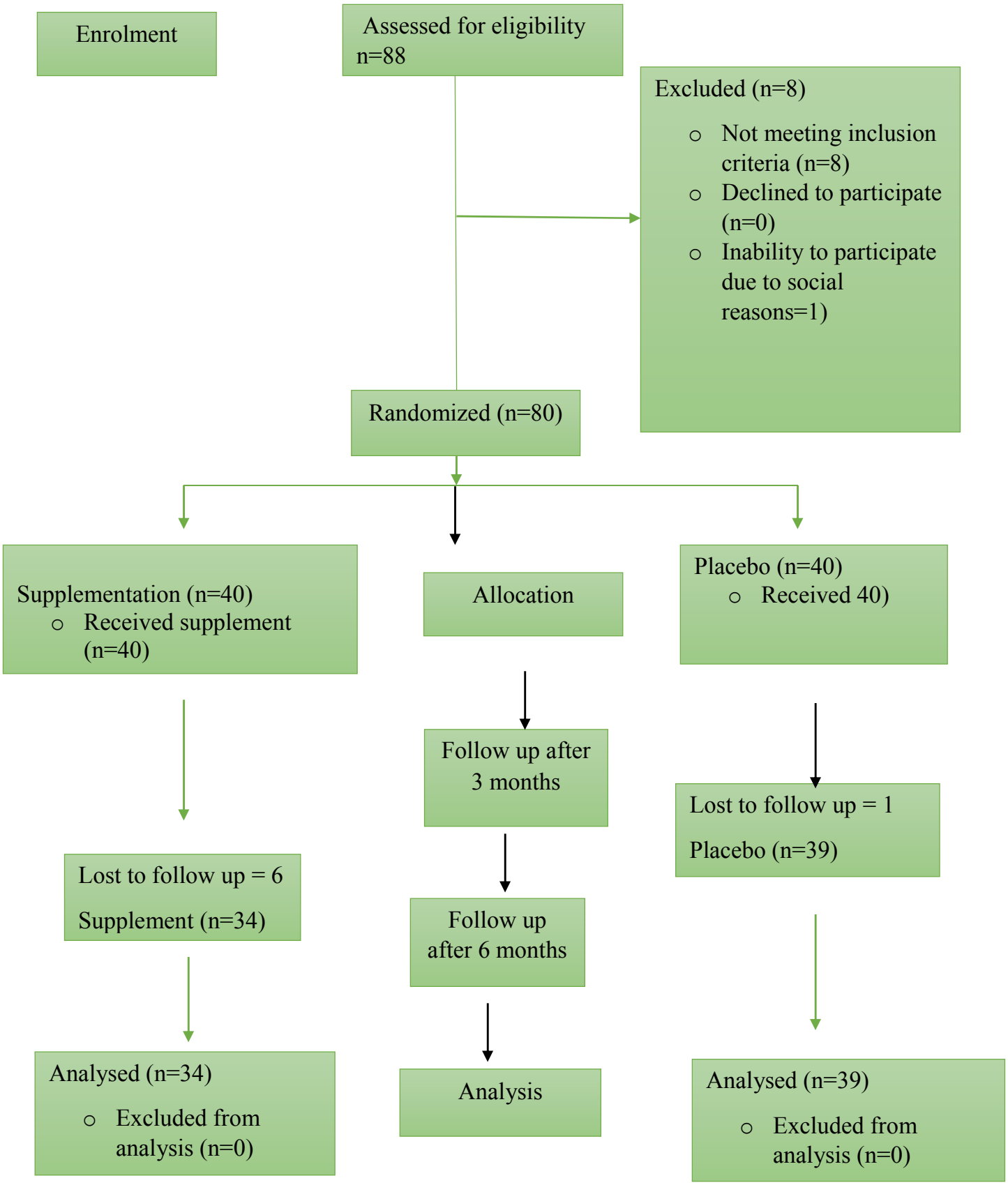
A total of 88 patients were identified through the various centres, to be eligible for recruitment. Eight of the 88 were excluded as they were unwilling to give blood samples, due to social reasons and due to the severity of the disease stage.

A total of 80 adolescents with HIV on HAART were recruited over a period of one month from 1st January 2015 to 30th January 2015. They were randomised into two arms of 40 each. As shown in the CONSORT flow chart (Figure-1) the observations were done for a period of six months from January 2015-June 2015.

Seven participants dropped out of the study by the end of 6 months, 6 from the supplementation group and 1 from the placebo group. Analysis at the end of 6 months was done on 34 patients in the intervention group and 39 patients in the placebo group.

Fig: 1

Recruitment, supplementation and analysis

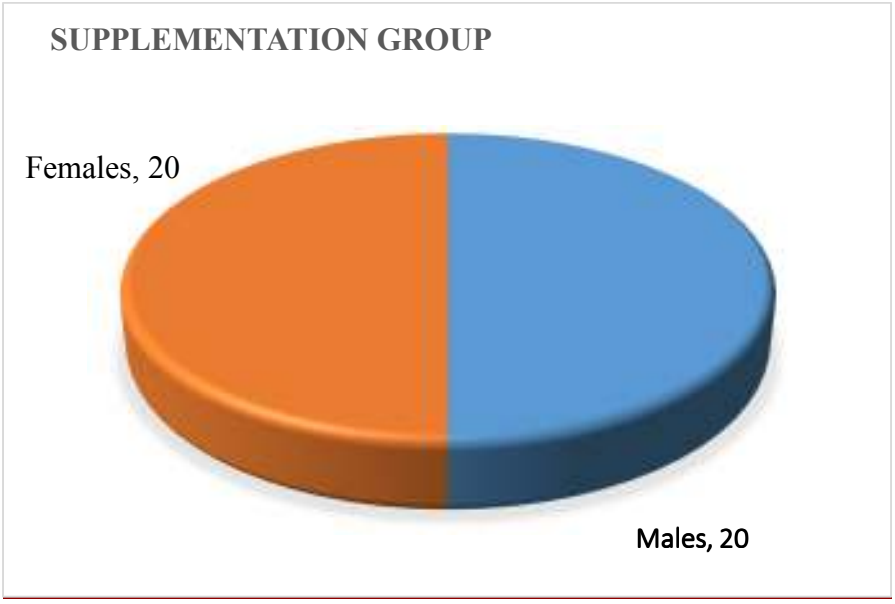


Demographic characteristics of supplementation and placebo groups.

Table 1: Gender distribution in supplementation and placebo groups.

Gender	Supplementation		Placebo	
	n	%	n	%
Male	20	50.0%	21	52.5%
Female	20	50.0%	19	47.5%

Fig2: Gender distribution in supplementation group



There were 50% males and 50% females in the supplementation group

Figure 3: Gender distribution in placebo group

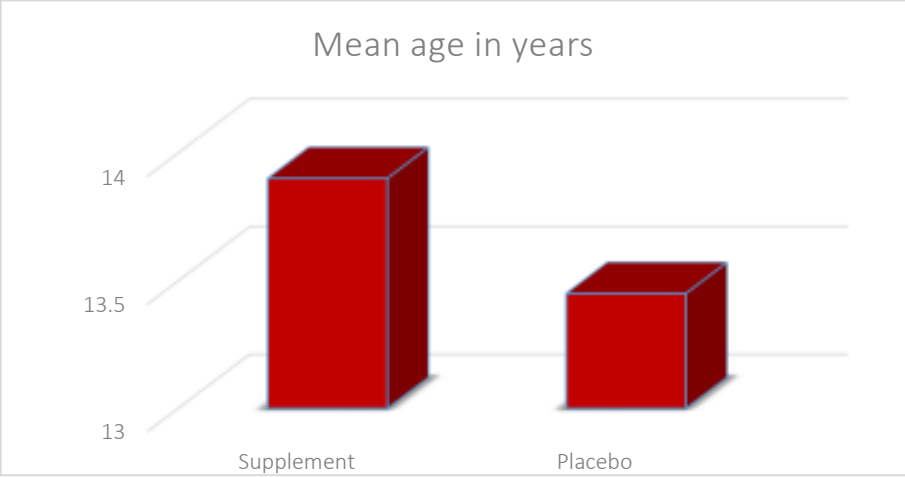
There were 52.7% males and 47.5% females in the placebo group

Table 2: Age distribution in the supplementation and placebo groups.

	Supplementation		Placebo	
Variable	Mean	SD	Mean	SD
Age (yrs)	13.90	2.706	13.45	2.591

The mean age in the supplementation arm was 13.9 years and 13.4 years in the placebo group

Fig 4: Age distribution in the Supplementation and Placebo groups



The mean age in the supplementation group was 13.9 ± 2 years and in the placebo group 13.4 ± 2 yrs.

BASELINE PARAMETERS:

Table 3: Baseline calorie and protein intake in the supplementation and placebo groups

Variables	supplementation		Placebo	
	Mean	SD	Mean	SD
Calorie (Kcal)	1507.58	219.142	1481.80	230.545
Protein (gm)	39.038	9.7868	40.105	8.1367

The mean calorie intake was 1507 kcal in the supplementation group and 1481 kcal in the placebo group.

The mean protein intake at baseline in the supplementation group was 39 gm and in the placebo group it was 40 gm.

Table 4: Baseline Vitamin deficiencies in the supplementation and placebo group

Vitamin Deficiency	supplementation		placebo	
	n	%	N	%
Present	07	17.5%	04	10.0%
Absent	33	82.5%	36	90.0%

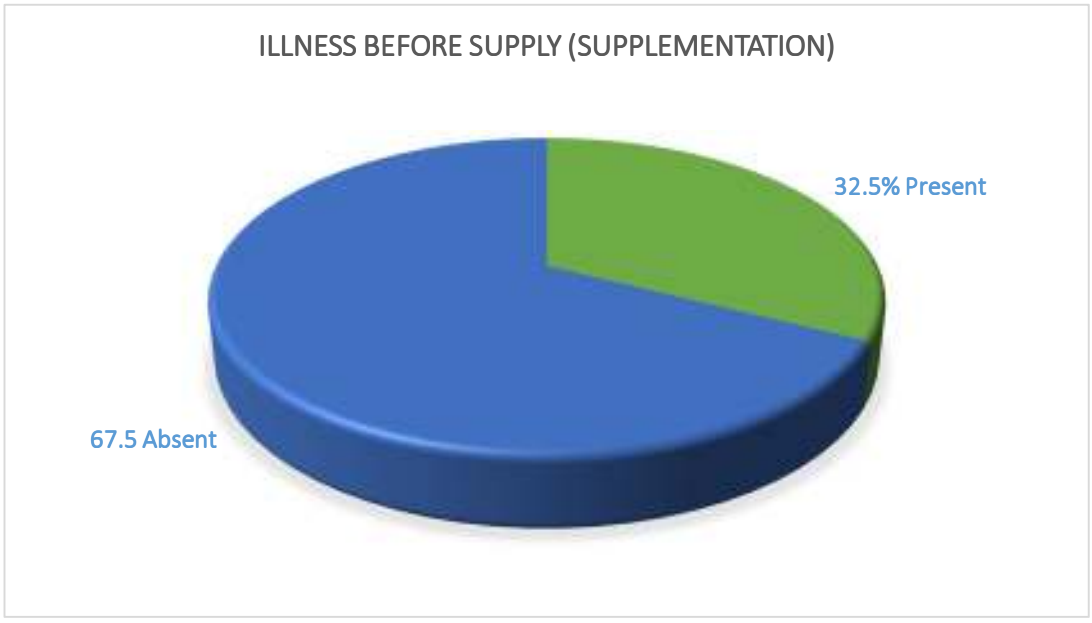
17% of the supplementation group and 10% of the placebo group had vitamin deficiencies at the start of the study.

Table 5: Number of participants in supplementation and placebo groups with illnesses before intervention

Illness before supplementation	supplementation		Placebo	
	N	%	n	%
Present	13	32.5%	8	20%
Absent	27	67.5%	32	80%

In the supplementation group, 13 participants (32.5%) and in the placebo group 8 (20%) had illnesses before start of study.

Fig: 5 Percentage of patients with and without illness before intervention in the supplement group



32.5% had illnesses before intervention in supplementation group.

Fig 6: Percentage of patients with and without illness before intervention in the placebo group.

20% of the patients had illnesses before intervention in the placebo group

Table 6: Baseline weight, height, and BMI in the intervention and placebo groups.

Variables	Supplementation		Placebo	
	Mean	SD	Mean	SD
Weight (kgs)	36.383	10.9010	35.560	10.3151
Height (cms)	149.48	12.858	148.65	12.301
BMI(kg/m^2)	16.570	2.3038	16.528	2.1254

The mean baseline weight was 36.3 kg in the supplementation group and 35.5 kg in the placebo group.

The mean baseline height was 149.5 cm in the supplement group and 148.7 cm in the placebo group.

The mean baseline BMI in the supplementation group was 16.5 kg/ m^2 and 16.5mg/ m^2 in the placebo group.

Table7: Baseline haemoglobin and fasting triglyceride levels in supplementation and placebo groups

Variables	Supplement		Placebo	
	Mean	SD	Mean	SD
CD4 (Mean ± SD) Cells/mm^3	678.80	274.282	723.15	228.119
Hemoglobin (gm/dl)	9.743	2.2513	10.760	2.0102
Fasting Triglyceride (mg/dl)	99.18	92.665	84.75	19.937

The mean baseline CD4 levels in the supplementation group was 678 cells/ mm^3 and 723 cells/ mm^3 in the placebo group.

The baseline haemoglobin levels in the supplementation group was 9.7 gm/dl and 10.7 gm/dl in the placebo group. The baseline fasting triglyceride levels in the supplementation group was 99 mg/dl and 84 mg/dl in the placebo group.

EFFECTS OF INTERVENTION AT THE END OF 3 MONTHS

Table 8: Weight, Height, and BMI at the end of 3 months in supplementation and placebo group

Variables	supplementation (n=38)		Placebo(n= 34)		p value
	Mean	SD	Mean	SD	
Weight (kgs)	37.479	9.5684	37.521	8.2236	0.748
Height (cms)	149.37	12.178	150.56	12.114	0.718
BMI (kg/m^2)	17.071	2.3576	16.532	1.7273	0.296

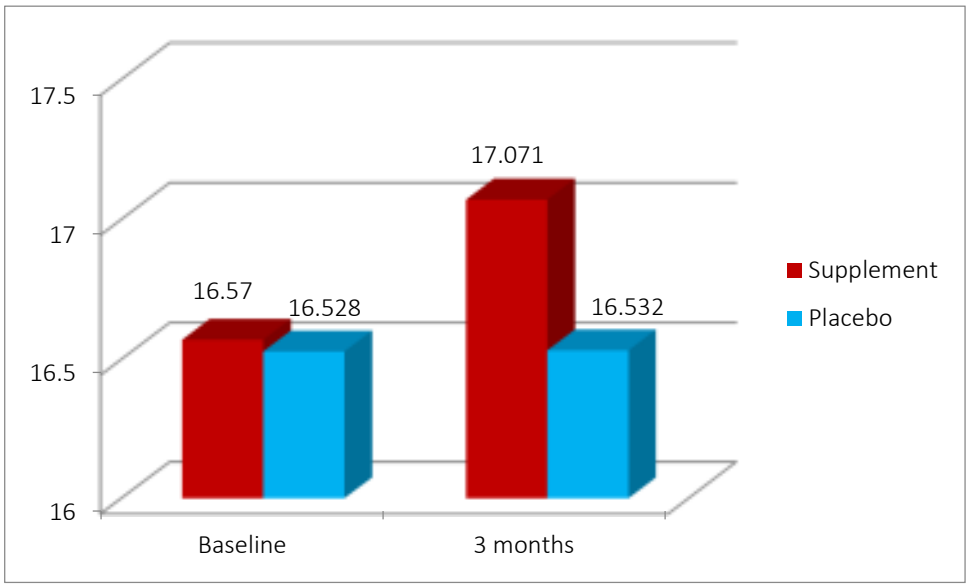
The mean weight at the end of 3 months in the supplementation group was 37.4 kg and in the placebo group 37.5 kg. (p value - 0.748).

The mean height in supplementation group was 149.4 cm and in placebo was

150.6 cm (p value-0.718).

The mean BMI at the end of 3 months was 17.1 kg/m^2 in supplementation group and 16.5 kg/m^2 in placebo group (p --0.296).

Figure 5: BMI at 3 months in supplementation and placebo group from baseline.



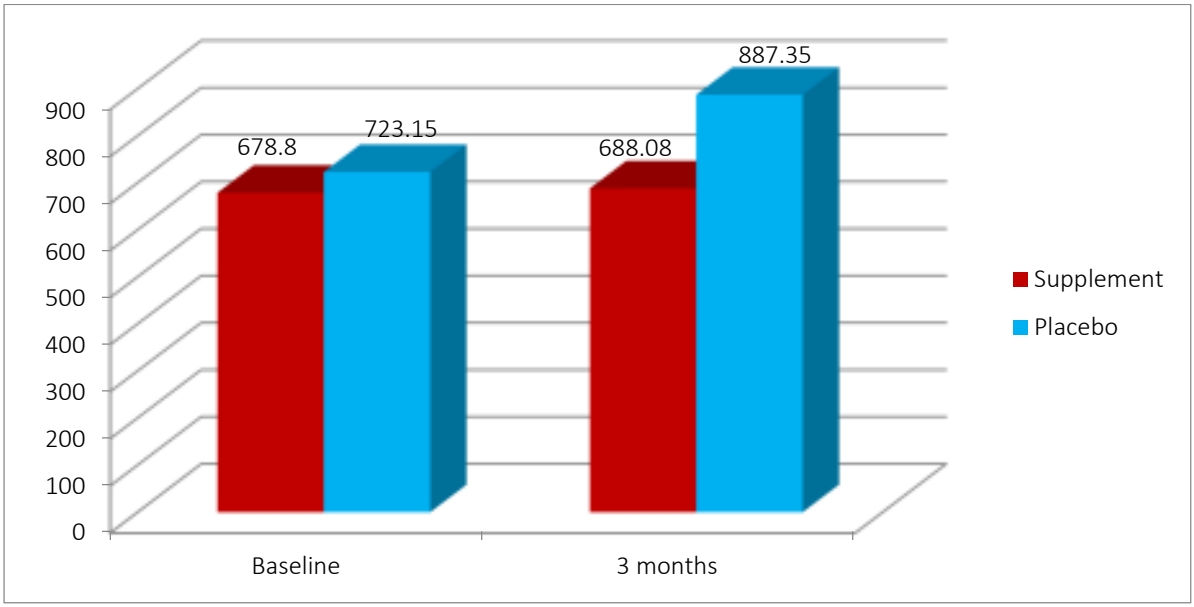
There was an increase in BMI of 0.6 kg/m^2 in supplementation group at the end of 3 months. In the placebo group the increase was 0.01 kg/m^2 at the end of 3 months.

TABLE 9: CD4 levels after 3 months in supplementation and placebo groups

CD4 Cells/mm^3	Supplementation (n=38)		Placebo(n= 34)		p value
	Mean	SD	Mean	SD	
	688.08	218.423	887.35	759.243	0.073

The mean CD4 levels at the end of 3 months is 688 cells/mm^3 in the supplementation group and 887 cells/mm^3 in the placebo group.

Figure 6: CD4 levels in supplementation and placebo groups from base line to 3mo.



The mean increase in CD4 levels at the end of 3 months in supplementation group was 7 cells/mm^3. The increase in the placebo group was 164 cells/mm^3.

Table 10: Weight, height and BMI at the end of 6 months

Variables	Supplementation (n=38)		Placebo(n= 34)		p value
	Mean	SD	Mean	SD	
Wt I (kg)	36.383	10.9010	35.560	10.3151	
Wt II (kg)	37.479	9.5684	37.521	8.2236	0.748
Wt III (kg)	39.655	8.4976	37.809	8.1259	0.230
Ht I (cm)	149.48	12.858	148.65	12.301	
Ht II (cm)	149.37	12.178	150.56	12.114	0.718
Ht III (cm)	149.84	11.767	150.74	11.915	0.795
BMI I (kg/m^2)	16.570	2.3038	16.528	2.1254	
BMI II (kg/m^2)	17.071	2.3576	16.532	1.7273	0.296
BMI III (kg/m^2)	17.537	2.3321	16.259	2.3957	0.036

Weights at the baseline (Wt I), 3 mo (Wt II) and 6 mo (Wt III) were 36 kg, 37 kg, and 39 kg respectively in the intervention group and 35 kg, 37.5 kg and 37.8 kg respectively in the placebo groups.

Heights at baseline (Ht I), 3 mo (Ht II) and 6 mo (Ht III) were 149.4cm, 149.3 cm and 149.8 cm respectively in the supplementation group and 148.6cm, 150.5cm and 150.7 cm respectively in the placebo group.

BMI at baseline (BMI I), 3 mo (BMI II) and 6 mo (BMI III) were 16.5 kg/m^2, 17.0 kg/m^2 and 17.5 kg/m^2 respectively in the supplementation group, and 16.5 kg/m^2, 16.5 kg/m^2 and 16.2 kg/m^2 respectively in the placebo group.

Table11: Increase in weight at the end of 3 months and 6 months

Weight gain	Supplement	Placebo	p value
At 3 months(kgs)	1.096	1.961	0.748
At 6 months(kgs)	2.175	0.281	0.230

Increase in weight at the end of 6 months is 2.175 in the supplementation group and 0.23o in placebo group.

Table 12: Increase in height at the end of 3 months and 6 months

Height gain	Supplement	Placebo	p value
At 3 months(cms)	0.11	1.91	0.718
At 6 months(cms)	0.47	0.18	0.795

Height increased by 0.47 cms at the end of 6 months in supplement group and by 0.18 cms in the placebo group.

Table 13: Increase in BMI at the end of 3 months and 6 months

BMI gain	Supplement	Placebo	p value
At 3 months kg/ m^2	0.501	0.004	0.296
At 6 months kg/ m^2	0.466	-0.273	0.036

The BMI at the end of 6 months is increased by 0.466 kg/m^2 in the supplement group whereas it was (-0.273) kg/m^2 in the placebo group. Therefore the difference between the arms in the BMI increase is significant with a p value of 0.036.

Fig 8: Comparison in weight at baseline, 3 months, 6 months between supplementation and placebo groups.

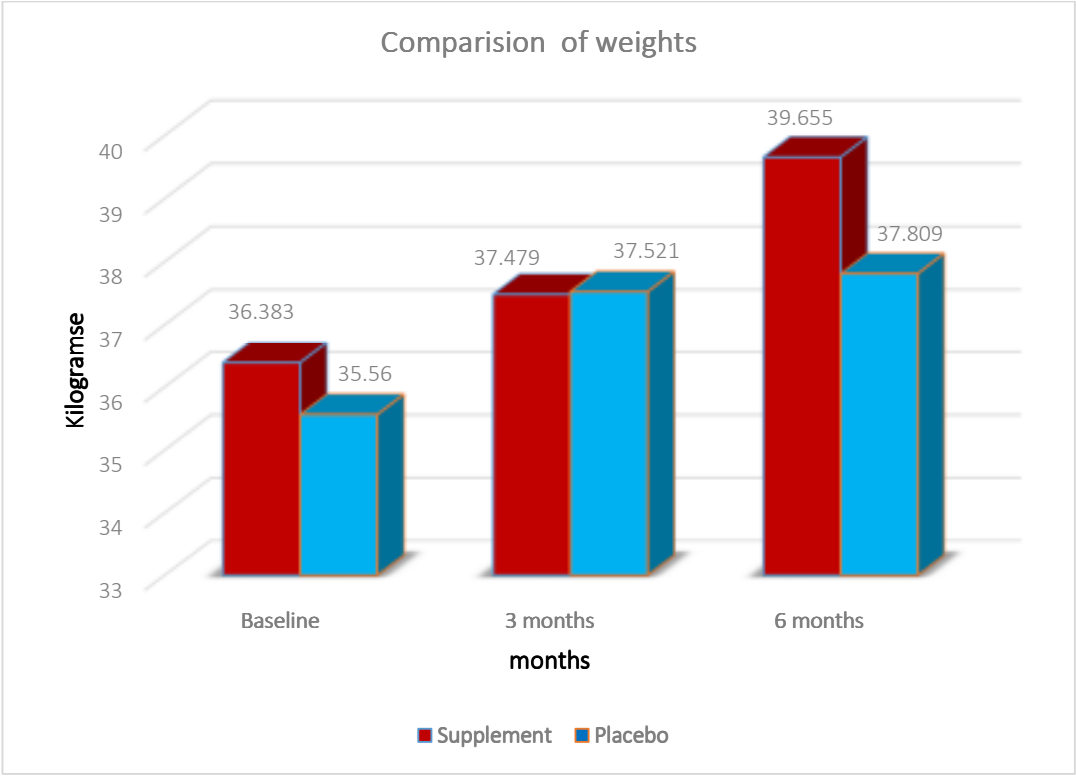
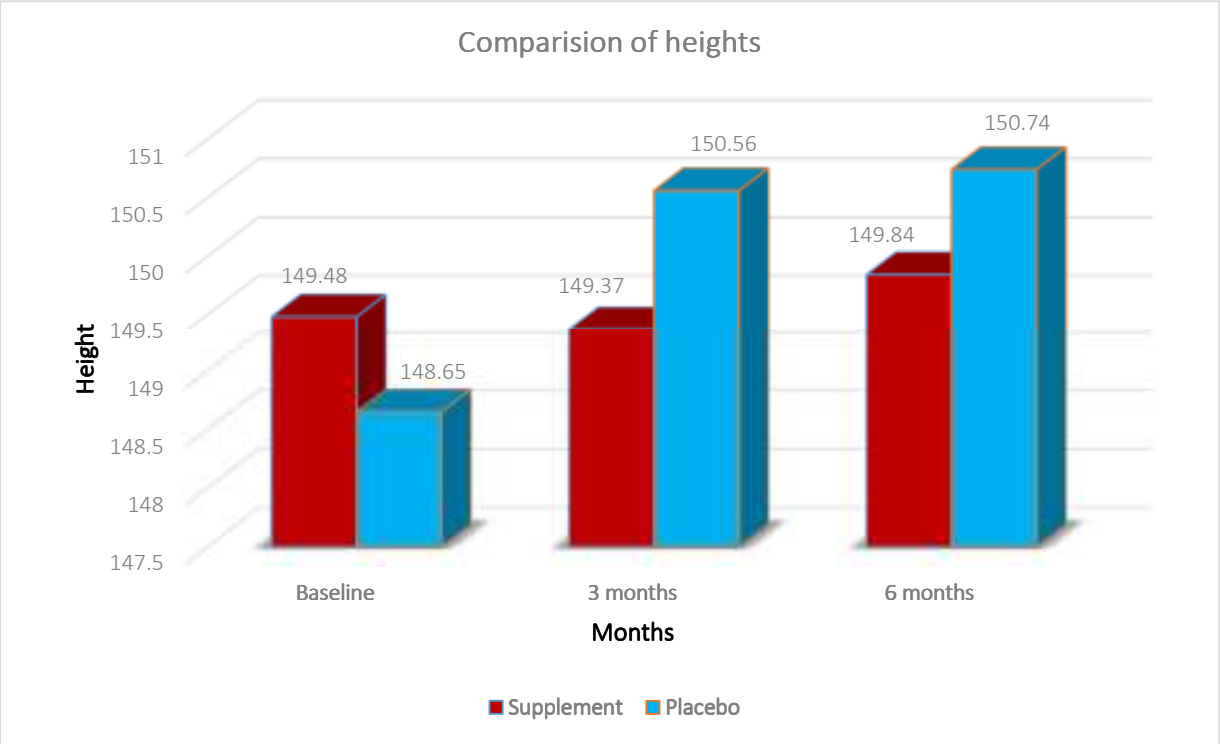
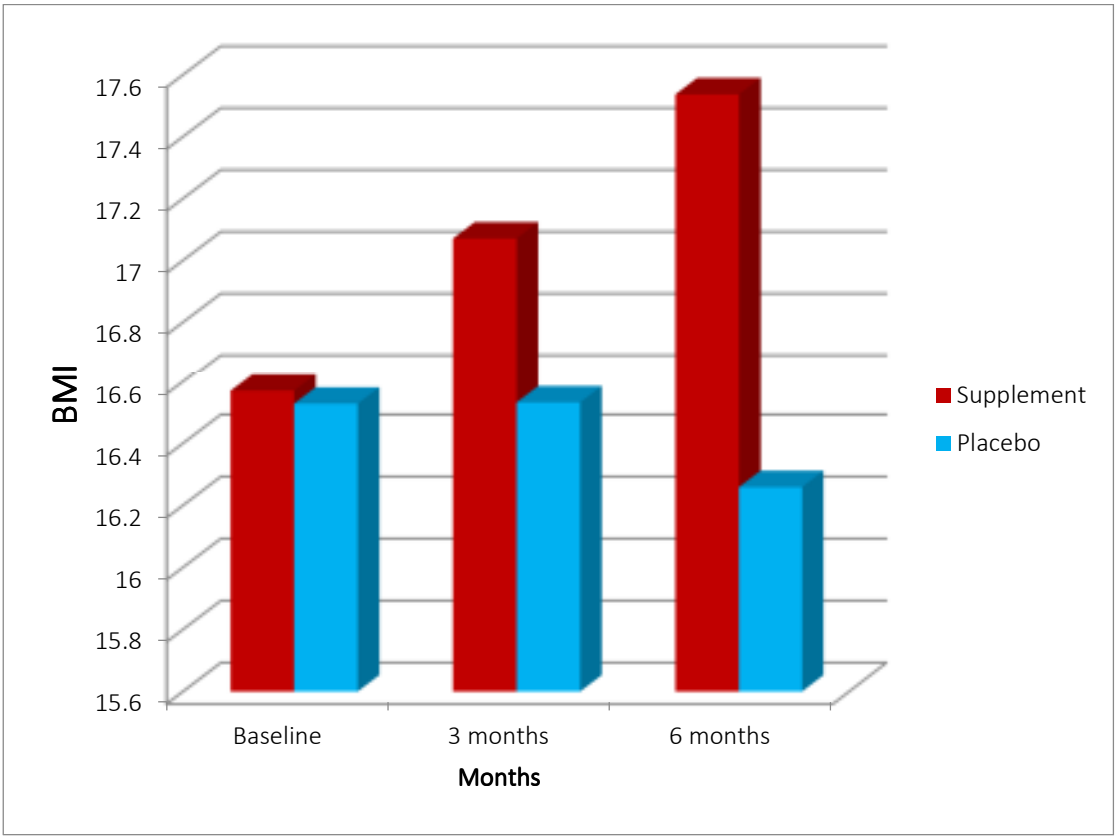


Figure 7: Height from baseline to 3 months and six months in both the arms.



Heights at baseline, after 3 months and after six months were 149.4cm, 149.3 cm and 149.8 cm respectively in the supplementation group, and 148.6cm, 150.5cm and 150.7 cm respectively in the placebo group.

Figure 8: BMI at baseline, after 3 months and after six months in both the arms.



Increase in BMI from baseline to after 6 months was 0.9 kg/$m^{2.}$ There was a decrease in BMI of 0.3 kg/m^2 in the placebo group from baseline to after 6 months. (p value - 0.036).

Table 11:CD4 levels at the end of 6 months in the supplementation and placebo group

Variables	Supplement(n=38)		Placebo(n= 34)		p value
	Mean	SD	Mean	SD	
CD4 (cells/mm3) (Baseline)	678.80	274.282	723.15	228.119	
CD4 (cells/mm3) >3mo	688.08	218.423	887.35	759.243	0.073
CD4(cells/mm3) >6mo	718.13	247.488	1219.65	1886.545	0.294

The CD4 levels at base line, 3 months and 6 months are 678 cells/mm3, 688 cells/mm3 and 718 cells/mm3 respectively in the intervention group. The increase in CD4 levels to be written herein the placebo group the CD4 levels were 723 cells/mm3, 887 cells/mm3 and 1219 cells/mm3 respectively at baseline, 3 months and six months.

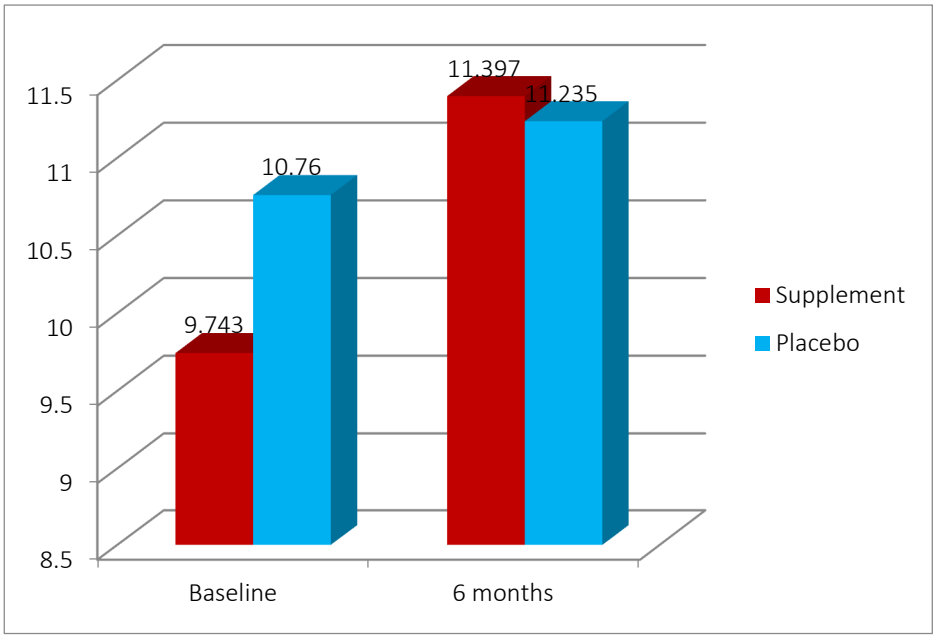
Table 12: Increase in CD4 levels at 3 months and 6 months

Variable	Increase at 3 m	Increase at 6 m	P value
CD4 (cells/mm3) >3mo	9.28	164.1	0.073
CD4(cells/mm3) >6mo	30.05	667.5	0.294

Table 12: Hemoglobin levels after 6 months in both the arms

Variables	Supplementation (n=38)		Placebo (n= 34)		P value
	Mean	SD	Mean	SD	
Hb (gm/dl) Baseline	9.743	2.2513	10.760	2.0102	
Hb (gm/dl) > 6 mo	11.397	1.6122	11.235	1.7953	0.660

Figure 10: Haemoglobin levels in supplement and placebo at 6 months from baseline



Hb levels increased from 9.7 gm/dl to 11.4 gm /dl in the supplement group and decreased from 11.3 gm/dl to 11.2gm/dl in Placebo group by the end of six months.

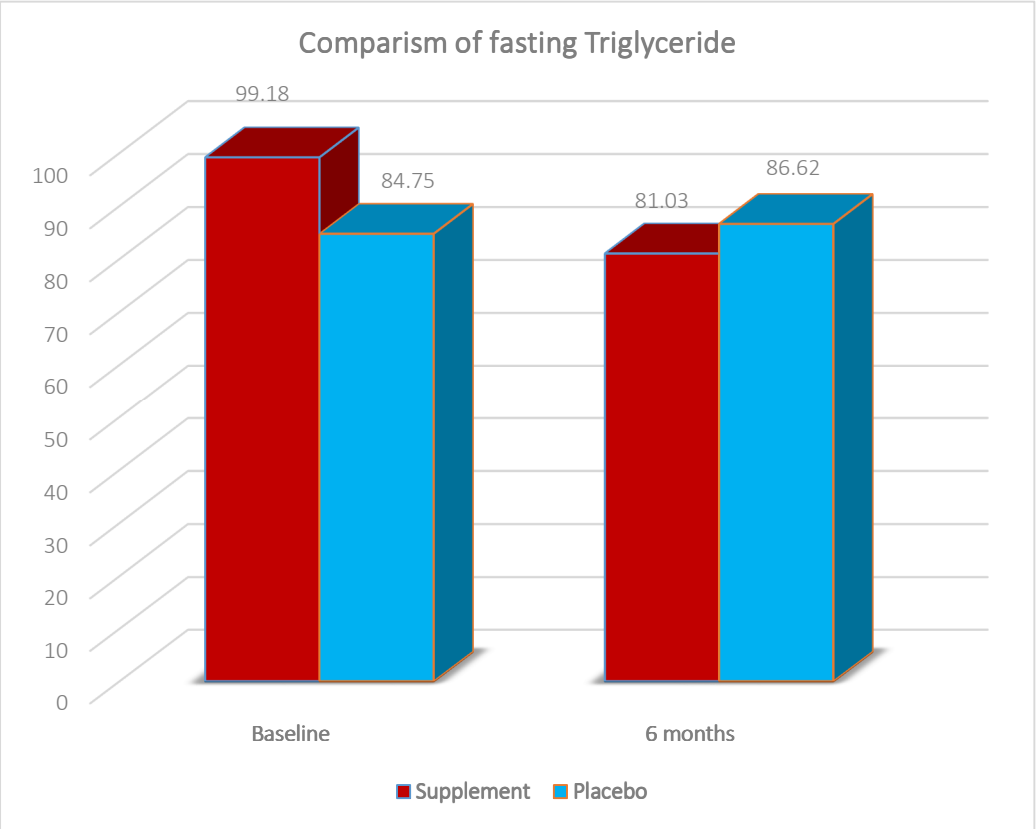
Table 13: Triglycerides at the end of 6 months in I supplementation and Placebo groups

Variables	supplementation (n=38)		Placebo(n= 34)		P value
	Mean	SD	Mean	SD	
Baseline Fasting triglycerides	99.18	92.665	84.75	19.937	
Triglycerides at six months	81.03	12.803	86.62	19.020	0.028

Baseline triglycerides in the intervention group was 99.1mg/dl and at the end of six months was 81.0mg/dl.

Bases line Triglycerides in the placebo group was 84.7 mg/dl and at the end of six months was 86.6 mg/dl

Figure 11: Triglyceride levels from baseline to six months in both intervention group and Placebo group.



The triglyceride levels decreased from 99.1mg/dl to 81 mg/dl in the supplementation group and increased from 81 mg/dl to 86.62 mg/dl in the placebo group which is statistically significant with a P value of 0.028 .This significance is comparing baseline to six months values.

Table 14:

Number of patients with illnesses before intervention and after intervention in both the arms.

	Variable	supplementation		Placebo	
		N	%	N	%
Illness before intervention	Present	13	32.5%	8	20%
	Absent	27	67.5%	32	80%
Illness after intervention	Present	0	0.0%	1	2.9%
	Absent	39	100.0%	33	97.1%

32.5% had illnesses in the supplementation group in before intervention and 20% in the placebo group had illnesses.

After intervention, at the end of six months none had illnesses in the supplementation group and 2.9% in the placebo group had illnesses.

Figure 12:

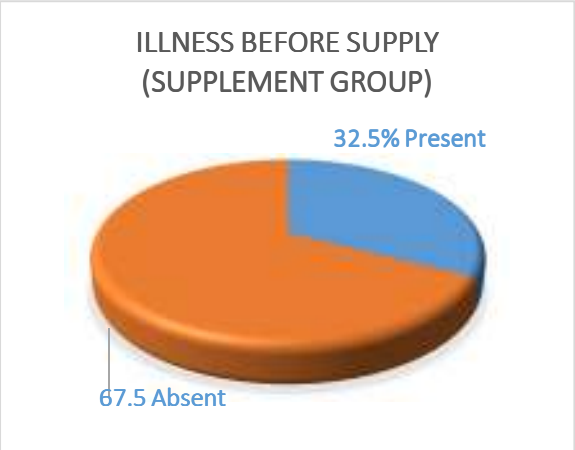


Fig 14

Figure 13:

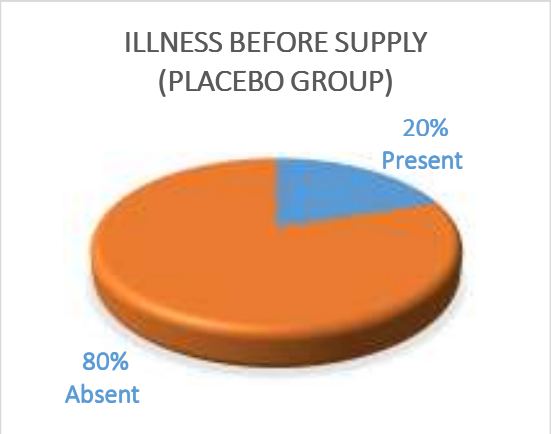
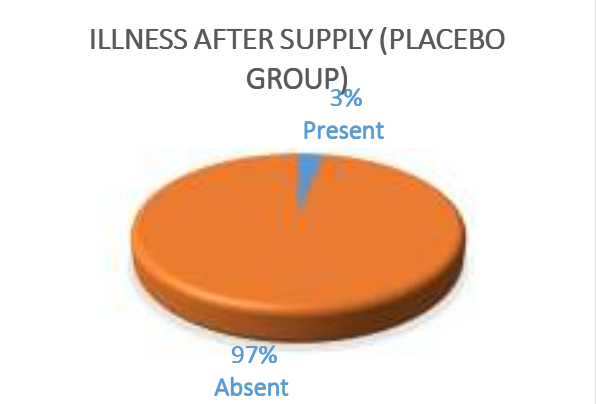


Fig 15



The percentage of illnesses dropped from 32.5% to 0 in the supplementation group and from 20% to 2.9% in the placebo group after intervention at the end of six months.

DISCUSSION

DISCUSSION:

Nutritional supplementation in adolescents with HIV and on HAART is a simple intervention with good impact on the overall outcome of illness. Several researchers have studied this strategy of nutritional intervention in effective management of patients with HIV / AIDS. Hence the two important caveats essential in managing patients with HIV / AIDS are:

a) Good compliance with antiretroviral therapy (ART) to prevent the spread of virus and to prolong life and

b) Optimal nutrition (99). The challenge is to apply both these principles of clinical care and nutrition science in the care of patients living with HIV / AIDS(119). This is a challenge because nutrition is generally emphasized very little, in the overall management.

A review of literature among studies done in the Indian subcontinent revealed that interventional studies among adolescents is limited. Studies on nutritional supplementation as an adjunct to HAART have not been replicated in the adolescent age group. There are not many studies on nutritional supplementation with micronutrients and macronutrients in adolescents. Furthermore there are no studies which reported the sustained effect of nutritional supplementation after discontinuation of nutrients.

From this study we have been able to conclude that there is a rise in CD4 levels after supplementation, in both arms though there was no statistically significant difference between the two arms. Next a significant increase in weight and BMI was noted in the

intervention group, while it was not so demonstrated in the placebo arm. This increase was sustained even after the withdrawal of supplementation.

Our study population is from in and around Vellore city in the southern state of Tamil Nadu, among patients who receive treatment from the ART centre, Christian Medical College, Vellore. CMC Vellore is an educational and research institute with a well-equipped tertiary care hospital in India. It is a premiere institution in the field of medicine in this country having national and international acclaim in several medical specialties. It is also one of the few autonomous institutions, founded in 1900 by Ida S Scudder, an American missionary doctor and continues to cater to poor and marginalised patients. CMC has been involved in the care of patients and families living with HIV / AIDS, from the beginning of HIV epidemic in 1986. The Anti-retroviral therapy centre (ART centre) cares for around 44,118 out patients and 2217 inpatients each year. An interdisciplinary Infectious disease clinic provides comprehensive care to 3873 patients with HIV / AIDS each year, as a collaborative venture involving various departments of Adult infectious disease, Paediatrics, Paediatric infectious disease(PIDC), Dermatology and Social work. Through the project ACTIFID(ACC,CMC TRUST FOR INFECTIOUS DISEASES) and the assistance of the National AIDS control organisation, Ministry of health and family welfare (NACO), ART drugs are provided free of cost to all the patients attending this clinic.

Most of our study population live in poor socio economic conditions. Studies have proven that there is a strong association between poverty and ill health. Richer countries and wealthier people enjoy a comparatively better state of health(120).

Many researchers have termed HIV as a “disease of poverty”. Poor health secondary to HIV causes increased demands on personal resources; ability to work and generate income becomes limited and this is the beginning of socio economic deterioration of affected families. Poor health conditions, inadequate access to good nutrition, inability to meet health expenses and unhealthy lifestyles are common challenges faced by patients with HIV. HIV leads to poverty, not only due to its health impacts, but also due to social impacts. The social stigma that is associated with HIV / AIDS discriminates against people in work places, in neighbourhood, as well as in health care centres(121). More than 60% of people living with HIV inhabit the world’s poorest regions like the Sub- Saharan Africa, Nigeria and India(122). It is a “vicious cycle”, where AIDS increases poverty and social deprivation, while poverty and social deprivation increase vulnerability to HIV infection(123).

Many of the patients in our study come from families where either or both parents have died. They are economically backward and hence have suboptimal nutrition. The financial burden on households living with HIV was 82% of income in the poorest quintile and just over 20% among the richest quintile(124). When the financial condition of these patients was assessed, it is striking to note that more than 60% of them live in extreme poverty. They live in huts made of mud with thatched roof, with no facilities for sanitation. Water source is the municipality water supply which is provided once or twice a week, when it is collected and stored in mud pots. Dietary habits are poor with many of them having rice three times a day with very minimal protein intake. All patients managed in this clinic are given a baseline nutrient

supplementation by the ART clinic. The staff repeatedly follow them up and emphasize on good diet as well as make efforts to address their problems.

Social stigma is another contributing factor for poor nutrition. Over the last decade, studies done in developing countries like South Africa, India and Nepal have revealed that adolescents who had lost either or both parents due to HIV were targets of stigma resulting in shame, poverty and disease. There is constant grief and general ill health among these adolescent patients which further worsens the disease outcome(125).

Having a population with a diverse socioeconomic and educational background, and with minimal or no understanding of the disease condition, it is a herculean task to initiate diet therapy as an adjuvant to medical therapy and to motivate patients to make regular visits to hospital in order to maintain adherence.

Of the total number of 80 patients enrolled in this study, there were 7 (17.5%) dropouts in spite of counselling them on the effects of nutrition. This included 6 (15%) from the supplementation group and 1 (2.5%) from the placebo group. Several efforts were made to ensure maximal participation during the study period, including regular reminders by telephone calls, reimbursing travel expenses, regular visits to their homes as reminders, by social workers who earlier had been caring for these families and monitoring compliance by regular recording in registers meant for this purpose. All their expenses were borne by the fluid research grant provided by the institution.

Baseline parameters were recorded including weight, height, body mass index, average daily calorie and protein intake by a dietician using a 24 hour recall method, haemoglobin, fasting triglyceride levels, CD4 levels, the number of illnesses and presence of vitamin deficiencies.

VITAMIN DEFICIENCIES:

At the start of this study, there were 7 patients in the supplementation group and 4 in the placebo group with vitamin deficiencies. Three patients had angular stomatitis and oral ulcers that responded to multivitamin supplementation. One patient had Bitot spots and one had night blindness, both responded to vitamin A supplementation. There was 1 girl with severe anaemia of 3 gm%, requiring hospitalisation and packed cell transfusion, followed later with oral iron therapy and dietary advice. Two others had Hb <6 gm/dl with low MCV (mean corpuscular volume); they were started on oral iron therapy. Three patients had poor dental hygiene, dental caries and vitamin D deficiencies with levels <3 ng/dl. They were treated at the hospital's dental department and also started on vitamin D supplements.

All the above patients were enrolled in the study and received standard of care treatment for the vitamin and iron deficiencies and the HAART regime. Since it was a double blinded study, neither the patient, family, social worker nor the treating team knew whether a patient was on placebo or the nutritional supplementation. The supplementation was given bimonthly in sealed packets.

DEMOGRAPHIC PATTERN:

AGE:

The mean age of the study population was 13 and a half years. According to WHO the adolescent age group is 10-19 yrs. Worldwide 25–30% of patients living with HIV / AIDS are adolescents, constituting 9–10 million population(28). And 45% of new HIV infections occur in the 13-22 year age group(29). Adolescence is a transition from a dependent childhood to an independent adulthood. Lack of impulse control, inability to make sound judgement, ignorance about consequences and inadequate access to healthcare are typical psychosocial features of the adolescent stage. Therefore during this phase, there is an increased vulnerability to high risk sexual behaviour and sexual ill health(36). HIV/AIDS might be a consequence of adolescent high risk behaviour.

Souza D T et al from Sao Paulo city have done a cross sectional study on 6-19 year old children and adolescents living with HIV / AIDS and receiving HAART, to assess their nutritional status. They reported an increased incidence of malnutrition in the adolescent age group. Luiz Carloz et al studied the body composition and nutritional status in 10-19 year old adolescents living with HIV and who were on HAART(126). They concluded in their study that recurrent infections and disease per se in these patients led to decreased lean body mass.

GENDER:

There were an equal number of males and females in the intervention and placebo arms in this study. A gender based discrepancy in nutritional intake, a deplorable common practise in India, was not a confounder here.

RESULTS:

CD4 LEVELS:

One of the objectives was to study the effect of nutritional supplementation on CD4 levels in adolescents with HIV on HAART. Several studies in the past have observed CD4 levels, as this indicates the overall outcome of any intervention undertaken on patients with HIV. Some studies reported a positive effect and others a negative effect.

One of the largest randomized controlled trials was done in Dar es Salaam, Tanzania by Fawzi et al enrolling as many as 1078 individuals with HIV and supplementing micronutrients in order to observe the effect on CD4 levels, (127). They concluded that nutrition supplementation led to increased weight, height, and Body mass index, as well as decrease in the number of opportunistic illnesses. The viral load decreased significantly with concomitant rise in CD4 and CD8 levels in the supplementation group. In our study the base line CD4 levels were comparatively lower in the intervention group. It was 678 in intervention arm and 723 in the placebo group. This is an important factor to consider because, earlier studies have demonstrated that the rise in CD4 levels depended on baseline CD4 levels(107). Having a low baseline CD4 levels is expected to show a slow rise in the levels even after supplementation.

At the end of 3 months there was an increase in the CD4 levels in both the groups, but more in the placebo group contradictory to what was expected. This could be explained by the low baseline CD4 count, which took a longer time to rise than the higher baseline CD4 levels noted in the placebo arm. It can also be concluded that the extremely low

baseline CD4 levels caused an increase in the number of illnesses in the supplementation group.

At the end of six months, CD4 levels showed a rise in both the arms, but more in the placebo arm, reasons for which are multifactorial. This rise in placebo group was not statistically significant.

After randomization, intervention group was found to be weaker with lower CD4 counts to start with and a higher prevalence of illnesses. By the end of 6 months there were more dropouts in the supplement group (15%) than in the placebo group (2.5%), resulting in a smaller sample size.

Great effort was taken to make the placebo and supplement powder to look and taste alike. A higher calorie and higher protein supplement might have been difficult to eat completely. Hence, compliance was questionable. Nutrition counselling was given to both groups on an equal footing. The degree of understanding and adherence is a personal choice and involves various factors; this might have also resulted in poor compliance. This could be another confounding factor. Sachdev et al in north India, in their study on adolescents with HIV reported that the literacy level of their study patients as well as their insight into disease played an important role in their nutritional status.(128) The stage of disease could also have a confounding factor in this study, leading to variable results(129).

WEIGHT, HEIGHT AND BMI

The mean baseline weight was 36.4 kg and 35.5 kg in the intervention group and placebo groups respectively. The mean BMI was 16.6 kg/m^2 and 16.5 kg/m^2 in the intervention and placebo groups respectively. At the end of 3 months, there was an increase in the mean weight and height of both groups. The mean weight in supplement group increased from 36kg to 37kg and in the placebo group from 35kg to 37kg. There was a similar increase in BMI in both the groups at the end of 3months. This increase is not statistically significant at the end of 3 months. However, it is of clinical relevance that regularly monitored supplementation with macronutrients and micronutrients will improve the nutritional status of adolescents with HIV on HAART.

By the end of 6 months, weight and BMI increased significantly in the supplementation group when compared with the placebo arm. There was a statistically significant rise in BMI from 16.5 kg/m^2 to 17.5 kg/m^2 in supplement group when compared to the placebo group, where it decreased from16.5 kg/m^2 to 16.3 kg/m^2 (p value - 0.036).

Therefore not just the HAART, but a nutritional supplementation in this group of adolescents with HIV / AIDS will improve BMI, an important predictor of mortality in HIV(82). A similar study by Vander Sande among adolescents concluded that a good BMI was a predictor of increased rate of survival in adolescent patients living with HIV(130).

HAEMOGLOBIN

There was a significant rise in haemoglobin level noted in the intervention arm from 9.7 gm% to 11.4 gm%; the rise in the placebo arm was not remarkable, from 10.8 gm% to 11.2 gm%. The difference in the rise in haemoglobin of 1.7 gm% in the supplementation arm as compared to that in the placebo arm of 0.4gm%, was not statistically significant (p value - 0.6). Chihurumnanya Alo et al to look at the effects of nutritional counselling and supplementation on the weight and haemoglobin levels of patients receiving HAART therapy in south east Nigeria. This study done on 84 patients, aged 18 – 25 years. These patients were randomized by simple randomisation, nutritional supplementation was provided for 6 months and its effects on Hb and BMI were assessed. They concluded that nutrition had a positive effect on haemoglobin. Hemoglobin in the supplementation group increased from 10.4 gm/dl to 12.1 gm/dl while in the placebo group it increased from 10.3 gm/dl to 11.2 gm/dl(p value - 0.0015)(131).

TRIGLYCERIDES

Baseline fasting triglycerides were done and after 6 months. Riddler et al reported that HAART caused a deranged lipid metabolism in the body. It can cause wasting of the peripheral fat and accumulation of central fat, cause insulin resistance thus contributing to a deranged lipid profile (132). Seven RCTs in which omega-3 supplementation (n=372) was given and four RCTs with dietary intervention (n=201) were conducted in the past ten years. A meta-analysis using random-effects models concluded that dietary intervention reduced triglyceride levels significantly when compared to the control group.

In our study, the mean baseline triglyceride levels in the intervention group was 99 mg% and was higher before the nutritional supplementation; in the placebo group it was 84mg%. After 6 months, a significant decrease in TG levels was noted, from a baseline value of 99mg% to 81mg% in the supplement group. The TG levels in the placebo group increased from the baseline. This difference between the intervention and placebo groups was statistically significant (p value - 0.028). This phenomenon has been explained by a concept. Nutritional supplementation decreases the adverse effects of HAART such as lipo-accumulation by lipolysis. The viral multiplication that occurs in HIV is promoted by malnutrition. Viral multiplication further causes several metabolic derangements like hypertriglyceridemia and lipogenesis. This can be controlled by supplementing good nutrition. (88) Furthermore triglycerides are inflammatory markers and therefore are elevated in a chronic condition like HIV(133). Nutrition supplementation is one of the adjuvant modality of treatment of HIV along with HAART. Therefore good nutrition leads to improving the disease condition, further decreasing the triglyceride levels which are considered one of the inflammatory markers of the disease.

MORBIDITY:

Georgiev et al have done a study to observe the effect of nutritional supplementation on the morbidity associated with HIV in terms of reduction of pneumonia, upper respiratory infections, acute gastroenteritis and the number of hospitalizations (134). Their studies have shown a significant reduction in the number of episodes of intercurrent infections and hospitalisations.

In our study at the baseline, number of patients with inter current infections and illnesses in the supplementation group were higher than in the placebo group. It was 13 out of 40 (32.5 %) in the supplementation arm and 8 out of 40 (20%) in the placebo arm. This could have been because of lower baseline CD4 levels in the intervention group to start with. After supplementation and at the end of 6 months, the number of patients with illnesses decreased from 32.5% to 0% in the supplementation group and from 20% to 2.9% in the placebo group. Kolofonos et al in their study on patients with HIV in Mozambique concluded that inadequate nutrition in HIV / AIDS led to increased susceptibility to opportunistic infections(135).

LIMITATIONS

LIMITATIONS OF THE STUDY

1) Confounding factors such as the disease stage, socioeconomic status, and level of education were present.
2) Baseline parameters like baseline CD4 levels, illness prevalence varied widely between the two arms.
3) Compliance could not be monitored more stringently.
4) There were more dropouts in the supplementation group than in the placebo group.
5) Frequency of illnesses was based on history from the caregivers and therefore might not have been reliable.

FUTURE DIRECTIONS FOR RESEARCH

FUTURE DIRECTIONS FOR RESEARCH

At the end of six months of study, which included 12 weeks of nutritional supplementation, we were able to conclude that supplementation had a beneficial effect on the overall health of patients living with HIV on HAART.

A longer duration of supplementation could be studied for benefits as another study.

A larger sample size could be used to replicate this study.

A cross over study could be done to add more strength to the study.

Physical activity in addition to nutritional supplementation in adolescents living with HIV is an area which has been demonstrated to have a positive effect by research conducted in other countries. This could be replicated among our adolescents.

CONCLUSIONS

CONCLUSIONS

1) Nutritional supplementation in adolescents with HIV and on HAART, leads to an increase in their weight and BMI..
2) There is an increase in hemoglobin level with supplementation in this group of adolescents.
3) There is significant decrease in the hypertriglyceridemia usually associated with HAART, when adolescents with HIV are given nutritional supplementation.
4) There is a significant decrease in morbidity among adolescents with HIV when nutritional supplementation is introduced for 3 months.
5) Macronutrient and micronutrient supplementation for 3 months, in adolescents with HIV on HAART does not increase CD4 count significantly.
6) Nutritional supplementation decreases morbidity in adolescents with HIV.

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ANNEXURES

Annexure 1

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD
CHRISTIANMEDICALCOLLEGE,
BAGAYAM, VELLORE 632002, TAMIL NADU, INDIA

Ref: FG/9117/10/2014 February 24, 2015

Mr. Robby Pria Sundersingh
The Treasurer
Christian Medical College,
Vellore.

Dear Mr. Robby Pria Sundersingh,

Sub: **Fluid Research Grant Project:**
Effect of micro and macro nutrient supplementation on the outcome of disease in adolescents with HIV on HAART.
Dr. Blessy Sucharitha, P.G Registrar, Child Health, Dr. Mona Basker, Paediatrics Unit III and Adolescent Medicine, Dr. Valsan P. Verghese, Child Health, Mr. Peace Clarence, Medicine Unit I, Dietetics, Dr. Rajesh Kannangai, Clinical Virology, CMC, Vellore.

Ref: IRB Min No: 9117 dated 15.10.2014

The Institutional Review Board at its meeting held on October 15th2014 vide IRB Min. No. 9117 accepted the project for a sum *25,000/- INR (Rupee Twenty Five Thousand only) will be granted for 18 months with the Account Head: 227464. Kindly arrange to release an additional amount of 20,000 INR (Rupee Twenty Thousand only)* to be operated by Dr. Blessy Sucharitha (blessysuchi@gmail.com) and Dr. Mona Basker (childh@cmcvellore.ac.in). *If overspent the excess should be debited from the respective departmental or Special funds.*

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
M.D. (Path.), D.N.B. (Path.), M.D. (Hospital Administration)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

CC: Dr. Blessy Sucharitha, Child Health, CMC, Vellore
Dr. Mona Basker, Child Health, CMC, Vellore
File

Annexure 2

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA.

Ethics Committee Registration No : ECR/326/INST/TN/2013 issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. Of India.

December 29, 2014

Dr. Blessy Sucharitha
P.G Registrar
Department of Child Health
Christian Medical College,
Vellore 632004

Sub: Study Title: "Effect of micro and macro nutrient supplementation on the outcome of disease in adolescents with HIV on HAART."
Dr. Blessy Sucharitha, P.G. Registrar, Child Health, Dr. Mona Basker, Paediatrics Unit III and Adolescent Medicine, Dr. Valsan P. Verghese, Child Health, Mr. Peace Clarence, Medicine Unit I, Dietetics, Dr. Rajesh Kannangai, Clinical Virology, CMC, Vellore.

Ref: IRB Min No: 9117 [INTERVEN] dated 15.10.2014

Dear Dr. Blessy Sucharitha,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed the following amendment for the study titled "Effect of micro and macro nutrient supplementation on the outcome of disease in adolescents with HIV on HAART" on December 29, 2014.

1. Request to include additional Co-investigator are Dr Priscilla Rupali, Professor and Head, Infectious Diseases, Medicine-I, Dr. Visali Jeyaseelan, Lecturer. Biostatistics.
2. Site of the study:
   a) Adolescent Medicine Unit, Paediatrics-III
   b) Paediatrics Infectious Diseases, Paediatrics-III
   c) ACTFID (ACC – CMC Trust for Infectious Diseases) ART centre, CMC Vellore and ID clinic, CMC, Vellore.
3. Study Type, Structured abstract, Publication Plans, Study design, Study subjects is revised.

Dr. George Thomas, D Ortho., Ph D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, M.Sc., Ph D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, B.Sc., M.A (S.W), M.Phil.,
Deputy Chairperson, Ethics Committee

Dr. Alfred Job Daniel, D Ortho, MS Ortho, DNB Ortho
Chairperson, Research Committee & Principal

Dr. Nihal Thomas,
MD., MNAMS., DNB (Endo), FRACP (Endo), FRCP (Edin), FRCP (Glasg)
Deputy Chairperson
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

The following Institutional Review Board (Silver Research & Ethics Committee) members reviewed the study proposal.

Name	Qualification	Designation	Affiliation
Dr. Alfred Job Daniel	D Ortho, MS Ortho, DNB Ortho	Principal, CMC. Chairperson-Research Committee, IRB.	Internal, Clinician
Dr. B. Antonisamy	M.Sc, PhD, FSMS, FRSS	Professor, Biostatistics, CMC, Member Secretary, Research Committee, IRB.	Internal, Statistician
Dr. L Jeyaseelan,	M. Sc, PhD, FRSS	Professor, Biostatistics, CMC.	Internal, Statistician
Dr. D.J. Christopher	B. Sc, MBBS DTCD DNB FRCP(Glasg) FCCP(USA)	Professor & Head, Pulmonary Medicine, Associate Director (HR), CMC.	Internal, Clinician
Dr. Thambu David	MBBS, MD, DNB	Professor & Head, Medicine, CMC.	Internal, Clinician
Dr. Asha Mary Abraham	MBBS, MD, PhD	Professor, Virology, CMC.	Internal, Clinician
Dr. Anuradha Bose	MBBS, DCH, MD,MRCP, FRCPCH	Professor, Child Health, CMC.	Internal, Clinician
Dr. B. Poonkuzhali	MSC, PhD	Professor, Haematology, CMC.	Internal, Basic Medical Scientist
Dr. Vinod Joseph Abraham	MBBS, MD, MPH	Professor, Community Medicine, CMC.	Internal, Clinician
Dr. Suresh Devasahayam	BE., MS, PhD	Professor of Bio-Engineering, CMC.	Internal, Basic Medical Scientist
Dr. Deepak Abraham	MBBS, MS	Professor, Endocrine Surgery, CMC.	Internal, Clinician

Dr. Sukriya Nayak	MBBS, MS	Professor, General Surgery, CMC	Internal, Clinician
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, CMC.	Internal, Clinician
Dr. Molly Jacob	MBBS, MD, PhD	Professor, Biochemistry, CMC.	Internal, Clinician
Dr. Anil Kuruvilla	MBBS, MD, DCH	Professor, Child Health, CMC.	Internal, Clinician
Dr. Sathya Subramani	Md. PhD	Professor, Physiology, CMC	Internal, Clinician
Dr. George Thomas	MBBS, D Ortho, Ph. D	Orthopaedic Surgeon, St. Isabella Hospital, Chennai, Chairperson, Ethics Committee, IRB.	External, Clinician
Prof. Keith Gomez	BSc, MA (S.W), M. Phil (Psychiatry Social Work)	Student counselor, Loyola College, Chennai, Deputy Chairperson, Ethics Committee, IRB	External, Lay Person & Social Scientist
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL	Sr. Legal Officer, CMC.	Internal, Legal Expert
Dr. P. Zachariah	MBBS, PhD	Retired Professor, Vellore	External, Scientist
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, Vellore	External, Scientist & Epidemiologist
Mr. C. Sampath	B. Sc, BL	Legal Expert, Vellore	External, Legal Expert

Rev. Dr. T. Arul Dhas	M.Sc, BD, DPC, PhD(Edin)	Chaplaincy Department, CMC.	Internal, Social Scientist
Dr. Binu Susan Mathew	MBBS, MD	Associate Professor, Clinical Pharmacology CMC.	Internal, Pharmacologist
Dr. Shirley David	M.Sc, PhD	Professor, Head of Fundamentals Nursing Department, CMC	Internal, Nurse
Dr. Vinitha Ravindran	PhD (Nursing)	Professor & Addl. Deputy Dean, College of Nursing, CMC, Vellore	Internal, Nurse
Mrs. Ruma Nayak	M.Sc (Nursing)	Professor, Head of Paediatric Nursing & Deputy Nursing Superintendent, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Nihal Thomas,	MD, MNAMS, DNB(Endo), FRACP (Endo) FRCP(Edin) FRCP (Glasg)	Professor, Endocrinology. Additional Vice Principal (Research), CMC. Deputy Chairperson, IRB, Member Secretary (Ethics Committee), IRB	Internal, Clinician

We approve the above amendment as presented.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD,MNAMS,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board
Christian Medical College, Vellore - 632 002.

Dr. Mona Basker, Paediatrics Unit III and Adolescent Medicine, CMC, Vellore.

IRB Min No: 9117 [INTERVEN] dated 15.10.2014

Annexure 3

Clinical Trial Details (PDF Generation Date :- Wed, 23 Sep 2015 00:45:30 GMT)

CTRI Number	CTRI/2015/08/006145 [Registered on: 31/08/2015] - **Trial Registered Retrospectively**
Last Modified On	19/08/2015
Post Graduate Thesis	Yes
Type of Trial	Interventional
Type of Study	Other (Specify) [nutritional suplementation]
Study Design	Randomized, Parallel Group, Placebo Controlled Trial
Public Title of Study	Effect of nutritional supplementation on the outcome of disease in adolescents with HIV on antiviral drug therapy
Scientific Title of Study	Effect of micro and macro nutrient supplementation on outcome of illness among adolescents with HIV on HAART

Secondary IDs if Any

Secondary ID	Identifier
NIL	NIL

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
Name	Blessy Sucharitha
Designation	PG Registrar
Affiliation	Christian Medical College
Address	Department of Paediatrics, Christian Medical College, Vellore, Christian Medical College, Vellore, Tamil Nadu Vellore TAMIL NADU 632004 India
Phone	9677607368
Fax	
Email	blessysuchi@gmail.com

Details Contact Person (Scientific Query)

Details Contact Person (Scientific Query)	
Name	Dr Mona Basker
Designation	Professor
Affiliation	Christian Medical College
Address	Paediatrics Unit III and Adolescent Medicine, Christian Medical College, Vellore Vellore TAMIL NADU 632004 India
Phone	04162283343
Fax	
Email	child3@cmcvellore.ac.in

Details Contact Person (Public Query)

Details Contact Person (Public Query)	
Name	Dr Mona Basker
Designation	Professor
Affiliation	Christian Medical College
Address	Paediatrics Unit III and Adolescent Medicine, Christian Medical College, Vellore Toothukudi TAMIL NADU 632004 India

	Age To	18.00 Year(s)
	Gender	Both
	Details	Adolescents from age 10-19 yrs diagnosed to have HIV and on HAART

Exclusion Criteria

Exclusion Criteria	
Details	1)People not falling in the age group of 10-19 yrs 2) Those already on micro and macronutrient supplements/ on any nutritional formula

Method of Generating Random Sequence	Computer generated randomization
Method of Concealment	Sequentially numbered, sealed, opaque envelopes
Blinding/Masking	Participant, Investigator, Outcome Assessor and Date-entry Operator Blinded

Primary Outcome

Outcome	**Timepoints**
Effect on CD4 levels	end of 3months April 2015 end of 6months July 2015

Secondary Outcome

Outcome	**Timepoints**
1.Effect on Height, Weight, Body Mass Index centiles, lipid profile 2. Number of episodes of illness over a period of 6 months	3 months 6 months

Target Sample Size	**Total Sample Size=**80 **Sample Size from India=**80
Phase of Trial	Phase 3
Date of First Enrollment (India)	06/01/2015
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years=**0 **Months=**6 **Days=**0
Recruitment Status of Trial (Global)	Not Applicable
Recruitment Status of Trial (India)	Completed
Publication Details	

Brief Summary

In clinical practice, highly active antiretroviral therapy (HAART), which aims at viral suppression, does not always result in complete immune recovery. The relationship between viral suppression and immune recovery is dynamic. Immune recovery in HIV infection and AIDS involves several factors like stage of the disease and socio economic factors etc. Of the socioeconomic factors, current nutritional status is believed to play a pivotal role.

Studies have revealed a high prevalence of nutrient deficiencies among children, adolescents and adults with HIV. Micronutrient and macronutrient supplementation among adolescents with HIV has been studied in several countries. Nutritional supplementation can be an easy and inexpensive

adjunctive therapy to delay progress of disease and to improve clinical outcome in HIV-infected persons in both developed and developing countries.

However, many centers in India catering to adolescents with HIV do not emphasize on the importance of nutrient supplementation along with HAART. In order to provide an emphasis on nutrition supplementation in addition to good compliance with medications, we propose to do an interventional study among this group of patients.

The primary aim of this study is to see the effect of supplementation for a 3 month period of both of micro and macronutrients, on CD4 lymphocyte counts and other parameters, to be assessed at the end of 3 months and 6 months. The secondary objective is to see if there is any improvement in weight, height, body mass index centiles, and triglyceride levels. A third objective is to assess quality of life in terms of number of episodes of illnesses and hospitalizations during the 6 month period.

Annexure 4

Christian Medical College, Vellore

Department of Paediatrics

Effect of micro and macro nutrient supplementation on disease outcome in adolescents with HIV on HAART

Information sheet to parents / patients.

You are being requested to allow your child to participate in a study to see the effect of micronutrients and macronutrient supplementation and the immunological outcome. We hope to include about 80 adolescents with HIV infection on HAART from 3 different centres in this study

1. Why are we doing the study?

HIV is a disease in which a person`s immunity against infection is compromised. HAART is a very effective way of restoring your child's immunity. But studies have shown that children on HAART are deficient in micronutrients and macronutrients. This deficiency delays the immune restoration by HAART.

Therefore we intend to support these deficient micronutrients and macronutrients to your child along with HAART and see if there is any added beneficial effect on immune outcome.

2. What is your role in the study?

If you agree to allow your child to participate in this study, we will take baseline details of your child like weight, height and number of illness in last 6 months in the form of questionnaire. We will also take blood sample for baseline CD4 levels at the beginning of the study. Then we will randomly divide the children into 2 groups where one group will receive micronutrients and macronutrient supplementation for 3 months along with HAART and the other group will receive only advice on nutrition without micronutrients and macronutrient supplementation.

We will reassess each child at the end of 3 months and 6 months and same parameters and CD4 counts.

Therefore your role in the study is to make sure your children enrolled in the study should be compliant with the micronutrients and macronutrient supplementation and regularly visit us for assessment.

3. **Will you have to pay for the blood test?**

You do not have to pay for the blood test.

4. Can you withdraw from this study after it starts?

Your child's participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your child's usual treatment at this hospital in any way.

5. How do I benefit from the study?

At the end of the study, if it is proven that micronutrients and macronutrient supplementation improves the outcome of HIV patients on HAART, we would recommend the nutrient supplementation along with HAART on a routine basis. It is a cost effective method of improving the efficacy of HAART.

6. Will your personal details be kept confidential?

The results of this study may be published in a medical journal or shared in a scientific meeting. However your child will not be identified by name in any publication or presentation of results. Patient's medical notes may be reviewed by people associated with the study, without your additional permission.

If you have any further questions, please ask If you have any further questions, please ask

Dr.P.Blessy Sucharita (0416-2283343)

Dr.Mona Basker(0416-2283343)

Dr.Valsan Verghese(0416 2283343)

Mr.Peace Clarence (**9894874799/0416 – 2282881**)

email: child3@cmcvellore.ac.in

அதில் முதலிரண்டிற்கு தொடர்ந்து அளிக்கப்படும். மற்ற
மூன்றிற்கு தொடர்ந்து கிடைக்காது மாவுச்சத்து வழங்கப்படும்.

அதன் பிறகு ஒன்று மாத இடைவெளியும் ஆறு மாத இடைவெளியும்
மேலும் சில சமயங்களில் CD4 எண்ணிக்கை பரிசோதனை
செய்யப்படும். ஆகையால் இந்த ஆய்வில் உங்கள் பங்கு
என்ன என்றால், இதில் பங்குபெறுவதில் பிரச்சனைகள் ஏதுமில்லை.
தொடர்ந்து உண்பதையும் மலம்பரிசோதனைக்கு தொடர்ந்து
வருவதையும் உறுதி செய்ய வேண்டும்.

3. நீங்கள் இரத்த பரிசோதனைக்கு பணம் செலுத்த வேண்டுமா?

நீங்கள் இரத்த பரிசோதனைக்கு பணம் எதுவும் செலுத்தத்
தேவையில்லை.

4. இந்த ஆய்வில் பங்கெடுப்பு என்பு விரும்பட முடியுமா?

இந்த ஆய்வில் உங்கள் பங்கு முற்றிலும் தன்னிச்சையானது.
நீங்கள் விரும்பினால் இதிலிருந்து எப்போது வேண்டுமானாலும்
விலகிக் கொள்ளலாம். இதனால் இந்த மருத்துவ மனையில் உங்கள்
வழக்கமான சிகிச்சை எந்தவிதத்திலும் பாதிக்காது.

5. இந்த ஆய்வினால் ஏற்படும் நன்மை என்ன?

இந்த ஆய்வின் முடிவு வரும்போது இந்த தொடர்புக்கு உங்கள்
இருதொற்றுக்கு பயன்படுத்தும் எனை உறுதி செய்யப்பட்டால் நாங்கள்
இந்த தொடர்புக்கு HAART சிகிச்சை முடிவு தொற்றுக்கு உட்படுவோர்
பரிந்துரை செய்வோம். ஆனால், இந்த ஆய்வுத்தொடர் 6 மாதம்
மட்டுமே நடைபெறுவதால் இருதொற்றுக்கு தர இயலாது.

6. உங்களிடம் தனிப்பட்ட விவரங்கள் பாதுகாக்கப் படுமா?

இந்த ஆய்வின் முடிவு ஏதும் மருத்துவ நாளிதழில் அல்லது
விஞ்ஞான கூட்டத்தில் பகிர்ந்து கொள்ளப்படலாம். உங்களிடம் கேட்கும்
அனுமதியின்றி உங்கள் விவரங்களும் ஆய்வின் முடிவுகளும்
தொடர்புடைய நிபுணர்களால் கவனிக்கப்படும். இதற்கு மட்டுமே இந்த
ஆராய்ச்சியில் கொடுத்த எண்ணை வைத்து.

இதற்கு இதற்கு தொடர்பு கொள்ளும் இடத்தை கீழ்கண்ட
முகவரியில் தொடர்பு கொள்ளவும்.

நன்றி.

நபரின் முழுவரை கையொப்பம் இடுங்கள் வேண்டாம்.

அதில் ஒருவரிடமிருந்து தொடர்ந்து அளிக்கப்படும். மற்ற
பரிமாணத்தில் தொடர்ந்து இல்லாத மாவுத்தூள் வழங்கப்படும்.

அதன் பிறகு முன்று மாத இடைவெளியும் அது மாத இடைவெளியும்
என்ன என்னவென்றால் CD4 எண்ணிக்கை பரிசோதனை
செய்யப்படும். ஆனையால் இந்த ஆய்வில் உங்கள் பங்கு
என்ன வென்றால், இதில் பங்குபெறுகிறீர் பின்னர் ஒருவருடம்
தொடர்ந்து உண்பதையும் மருத்துவரை சந்திக்க தவறாமல்
வருவதையும் உறுதி செய்ய வேண்டும்.

3. நீங்கள் இந்த பரிசோதனைக்கு பணம் செலுத்த வேண்டுமா?

நீங்கள் இந்த பரிசோதனைக்கு பணம் எதுவும் செலுத்த
தேவையில்லை.

4. இந்த ஆய்வில் பங்கேற்பது பின்பு விலக முடியுமா?

இந்த ஆய்வில் உங்கள் பங்கு முற்றிலும் தன்னிச்சையானது.
நீங்கள் விரும்பினால் இதிலிருந்து எப்போது வேண்டுமானாலும்
விலகிக் கொள்ளலாம். இதனால் இந்த மருத்துவ மனையில் உங்கள்
வழக்கமான சிகிச்சை எந்த விதத்திலும் பாதிக்காது.

5. இந்த ஆய்வினால் ஏற்படும் நன்மை என்ன?

இந்த ஆய்வின் முடிவு வரும்போது இந்த தொடர்ந்து உங்கள்
இதயத்தை பலப்படுத்தும் என உறுதி செய்யப்பட்டால் நாங்கள்
இந்த தொடர்ந்த HAART சிகிச்சை யுடன் ஒன்றாக உடனடியாக
பரிந்துரை செய்வோம். ஆனால், இந்த தொடர்ந்த மருந்தும்
முழுமையாக இதற்கானது தான் இயலாது.

6. உங்களின் தனிப்பட்ட விவரங்கள் பாதுகாக்கப்படுமா?

இந்த ஆய்வின் முடிவு ஏதும் மருத்துவ நாளிதழில் அல்லது
விஞ்ஞான கூட்டத்தில் பகிர்ந்து கொள்ளப்படலாம். உங்களின் வயது
அடையாளம் உங்கள் விவரங்களும் ஆய்வின் முடிவுகளும்
ரகசியம் காப்பதாக்கானது கவனமாகவும். நிச்சயமாக இந்த
ஆராய்ச்சியில் மட்டும் கொண்டு செல்லப்படும். 'முன்பு'
இதற்கான தனிக் குறிப்பு எதுவும் இருந்தால் இதற்கான
நபரிடம் முறையாக கலந்திட நீங்கள் வேண்டும்.

Annexure 5

Study Title: EFFECT OF MICRO AND MACRONUTRIENT SUPPLEMENTATION ON DISEASE OUTCOME IN ADOLOSCENTS WITH HIV ON HAART.

A RANDOMISED CONTROL TRIAL –INTERVENTIONAL STUDY

Study Number:

Participant's name:

Date of Birth / Age (in years):

I_____

_____,

Parent

of_____

___

(Please tick boxes)

Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]

I also understand that my child's participation in this study is entirely voluntary and that I am free to withdraw permission for my child to continue to participate at any time without affecting my child's usual treatment or his/her legal rights [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my child's health records even if I withdraw from the trial. I agree to this access [ ]

I understand that my child's identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree for my child to take part in this study.

Thumb impression

Signature:

Date:

Name**:**

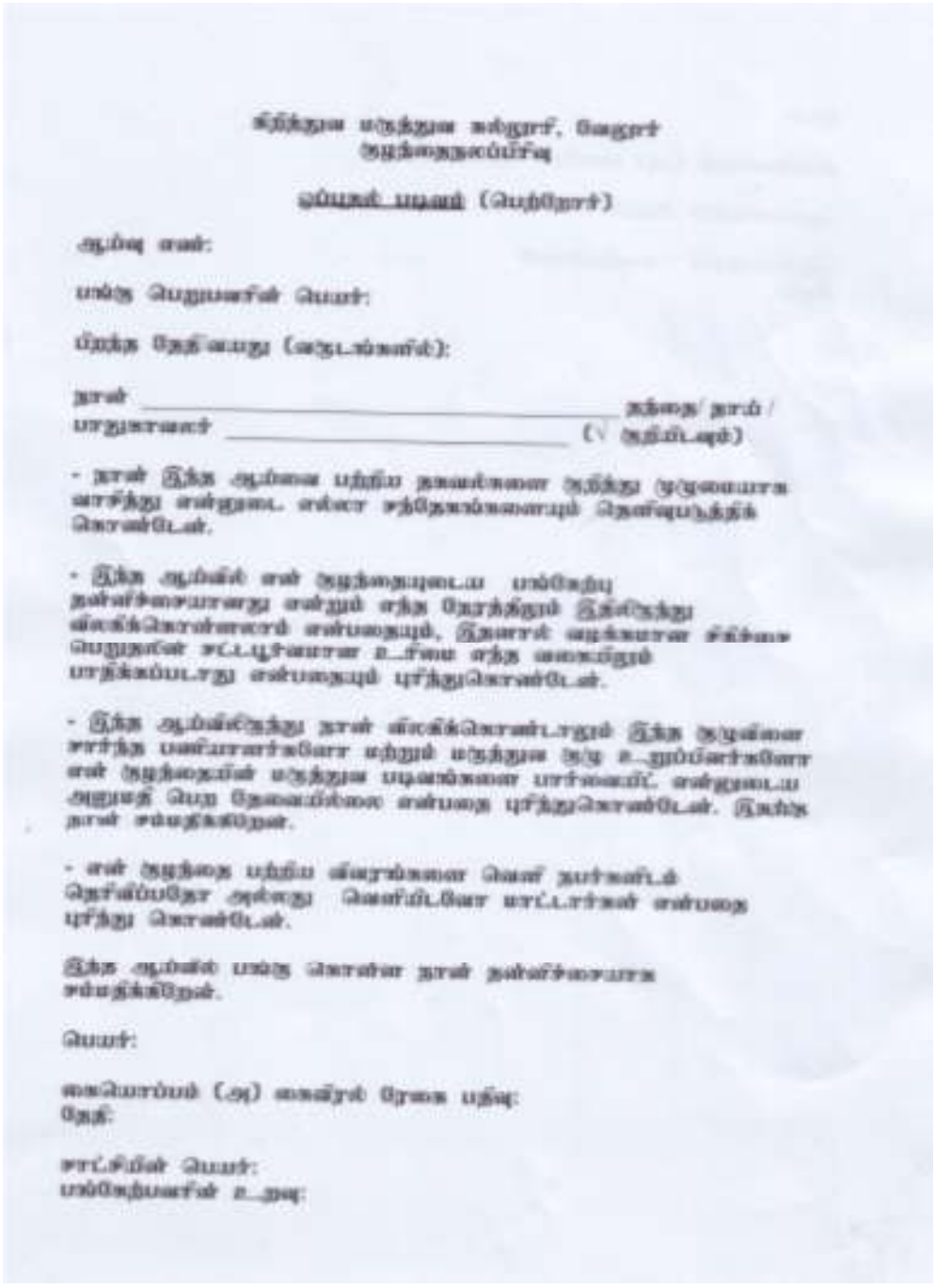
Relation to the patient

Name of witness and signature

Relation to participant:

Date:

Annexure 5 Tamil



கற்கை மருத்துவ அலுவர், வவுனர்
ஆத்மாதுகாப்பீடு

மாதிரி படிவம் (மருத்துவர்)

ஆய்வு எண்:

பங்கு பெறுபவரின் பெயர்:

பிறந்த திகதியது (வருடம்/மாதம்):

நான் _____ கற்கை/ நாம் /
பாதுகாவலர் _____ (✓ குறியிடுக)

- நான் இந்த ஆய்வை பற்றிய தகவல்களை தந்து முழுமையாக விளக்கப் பட்டுள்ளது. என்னை சந்தேகங்களையும் தெளிவுபடுத்தி கொண்டேன்.

- இந்த ஆய்வில் என் ஆத்மாதமுடைய பங்கேற்பு தன்னிச்சையானது என்றும் எந்த நேரத்திலும் இதிலிருந்து விலகிக்கொள்ளலாம் என்பதையும், நிபுணர் வழங்கிய சிகிச்சை பெறுவதில் சட்டபூர்வமான உரிமை எந்த வகையிலும் பாதிக்கப்படாது என்பதையும் புரிந்துகொண்டேன்.

- இந்த ஆய்வில்இருந்து நான் விலகிக்கொண்டாலும் இந்த ஆய்வை சார்ந்த மனிதர்களோ மற்றும் மருத்துவ நபு உறுப்பினர்களோ என் ஆத்மாதத்தில் மருத்துவ பராமரிப்பை பாதிக்காமல் என்னுடைய அனுமதி பெற்ற தகவல்களை என்னை புரிந்துகொண்டேன். இதற்கு நான் சம்மதிக்கிறேன்.

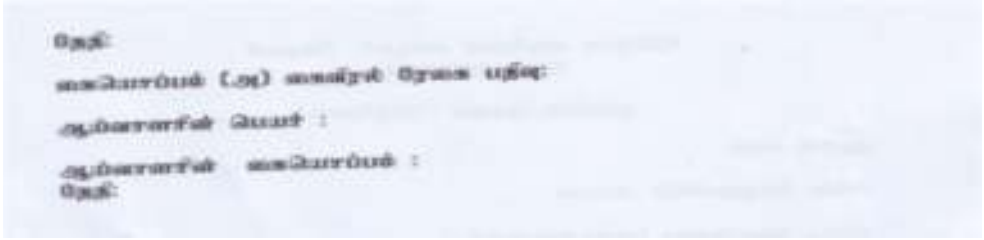
- என் ஆத்மாத மற்ற விபரங்களை வெளி நபர்களிடம் தெரிவிப்பதை அல்லது வெளியிடுவதை மாட்டார்கள் என்பதை புரிந்து கொண்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள நான் தன்னிச்சையாக சம்மதிக்கிறேன்.

பெயர்:

கையொப்பம் (அ) கைரேகை பதிவு:
திகதி:

சாட்சியின் பெயர்:
பங்கேற்பாளரின் உறவு:



திகதி:

கையொப்பம் (அ) கைரேகை பதிவு:

ஆய்வாளரின் பெயர் :

ஆய்வாளரின் கையொப்பம் :
திகதி:

Annexure 6

ASSENT TO TAKE PART IN A CLINICAL TRIAL

Study Title: EFFECT OF MICRO AND MACRONUTRIENT SUPPLEMENTATION ON DISEASE OUTCOME IN ADOLOSCENTS WITH HIV ON HAART.

A RANDOMIZED CONTROL TRIAL - INTERVENTIONAL TRIAL

.

Study Number:

Participant's name:

Date of Birth / Age (in years):

I_____,

daughter/ son

of_____

(Please tick boxes)

Declare that I have read the information sheet provided to me regarding this study and have clarified any doubts that I had. [ ]

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw / to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access.

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree for my participation to take part in this study.

Verbal Assent given by the patient Yes /No

Signed assent

Name:

Thumb impression/ Signature

Date:

Name of witness:

Relation to participant:

Date

Annexure 7

DATA PROFORMA

Effect of micro and macro nutrient supplementation on outcome of illness among adolescents with HIV on HAART.

Study number:

Age (yr): **Sex : F / M**

Disease stage: **Yr of diagnosis:** **Date of start of HAART:**

Physical exam findings (eg- vitamin deficiencies, Systems exam):

_____
_____
_____
_____

Dietary intake

	24 hour recall	**24 hr + baseline Supplement 70 Kcal & ___gm protein**
Calories / day		
Protein(gm)/ day		

No.	**Criteria**	**Baseline (Date)**	**3 mo f/u (Date)**	**6 mo f/u (Date)**
1.	Weight (kg)			
2.	Height (cm)			
3.	BMI (kg/cm2)			
4.	BMI centile (WHO)			
5.	CD4 count (/cu.mm)			
6.	Hb (gm%)		XXX	
7.	Fasting triglyceride		XXX	
8.	Illnesses (past 6 mo)		XXX	
9.	No. hosp adms(past 6 mo)		XXX	

Blessy, the following is for your notebook, so don't print this.

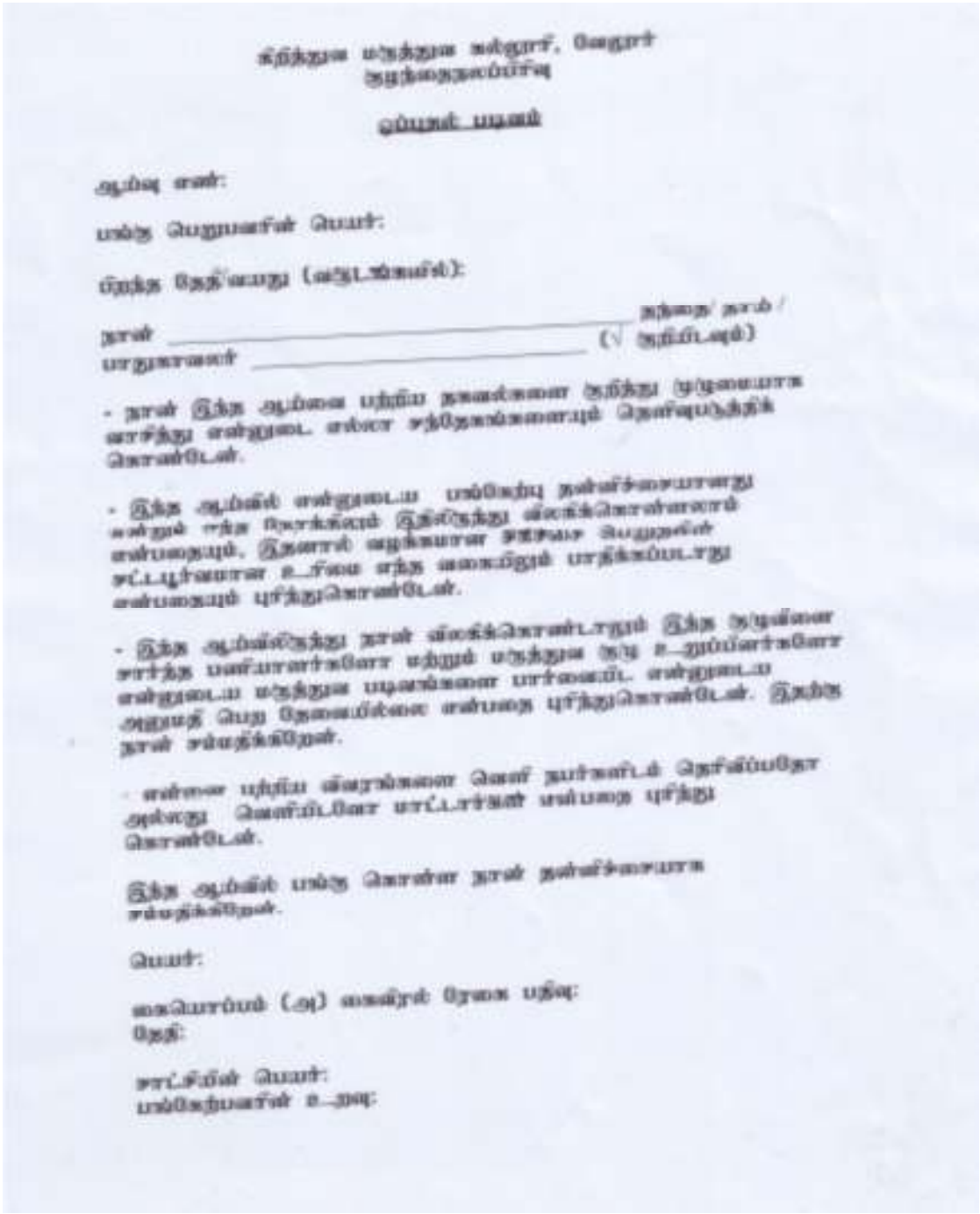
Study number: **Name:** **Hosp No :**

Age (yr): **Sex : F / M**

Address :

Phone number(s) :

Annexure 8



கிளிநொச்சி மாவட்ட சுற்றுலா, வேலைவாய்ப்பு
அபிவிருத்தி அமைப்பு

முன்மொழிவுப் படிவம்

ஆய்வு எண்:

பங்கு கொள்ளுனரின் பெயர்:

பிறந்த திகதி/வயது (அடையாளச் சீட்டின்படி):

நாள் _____ திகதி/ நாள் /
பாதுகாவலர் _____ (√ குறியிடவும்)

- நான் இந்த ஆய்வை பற்றிய தகவல்களை நன்கு புரிந்து கொண்டேன் என்னுடைய எல்லா சந்தேகங்களையும் தெளிவுபடுத்திக் கொண்டேன்.

- இந்த ஆய்வில் என்னுடைய பங்களிப்பு தன்னிச்சையானது என்றும் எந்த நேரத்தும் இதிலிருந்து விலகிக்கொள்ளலாம் என்பதையும், இதனால் எனக்கான சேவை வழங்கலில் எவ்வித பாதிப்பும் ஏற்படாது என்பதையும் புரிந்துகொண்டேன்.

- இந்த ஆய்வில் நான் வெளிக்கொண்டாலும் இந்த ஆய்வின் சார்ந்த பணியாளர்களோ அல்லது மருத்துவ நிபுணர்களோ என்னுடைய மருத்துவ பதிவுகளை பார்வையிட, என்னுடைய அனுமதி வேறு நோக்கங்களை என்பதை புரிந்துகொண்டேன். இதற்கு நான் சம்மதிக்கிறேன்.

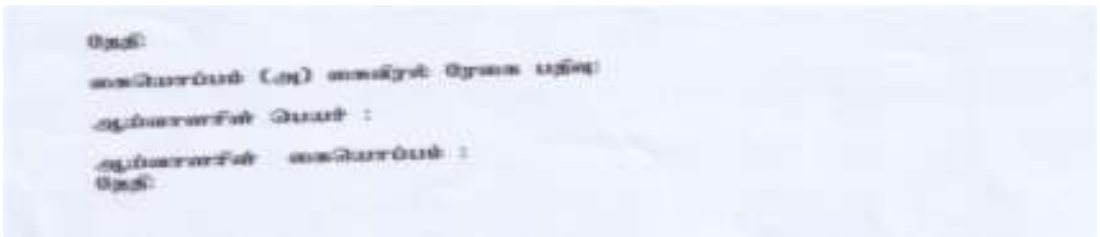
- என்னை மற்ற விசாரணைகளை வெளி நபர்களிடம் தெரிவிப்பதை அல்லது வெளியிடுவதை மாட்டார்கள் என்பதை புரிந்து கொண்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள நான் தன்னிச்சையாக சம்மதிக்கிறேன்.

பெயர்:

கையொப்பம் (அ) கைரேகை முகவர் முறைய பதிவு:
திகதி:

சாட்சியின் பெயர்:
பங்கேற்பாளரின் உறவு:



திகதி:

கையொப்பம் (அ) கைரேகை முகவர் முறைய பதிவு:

ஆய்வாளரின் பெயர் :

ஆய்வாளரின் கையொப்பம் :
திகதி: